

Novel Synthesis of Arylethynyl-Heterocycles

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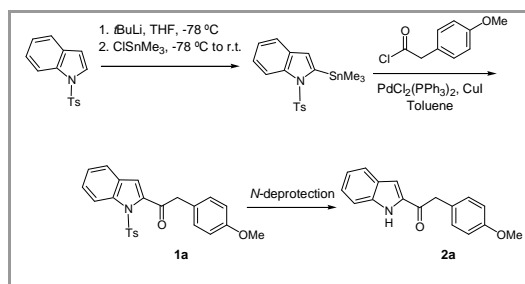
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Abstract: A new and easy synthesis of 2-arylethynyl-indole and 2-arylethynyl-pyrrole is described. *N*-deprotection and subsequent base-catalyzed elimination of *N*-tosylheteroaryl benzyl ketones are the key steps of the process.

Key words: acetylenes, indole, pyrrole, elimination, tosyl protecting group

The tosyl group has been one of the most commonly used groups to protect, activate and chelate indoles for lithiation at position 2.¹ In the course of one of our synthetic programs, 1-tosyl-2-(*p*-methoxyphenylacetyl)indole (**1a**) was prepared in excellent yields starting from *N*-tosylindole by 2-lithiation, transformation of the resulting 2-lithio derivative into the 2-trimethylstannyldole² derivative, and finally, Pd(0) catalyzed cross-coupling with *p*-methoxyphenylacetyl chloride³ (Scheme 1).



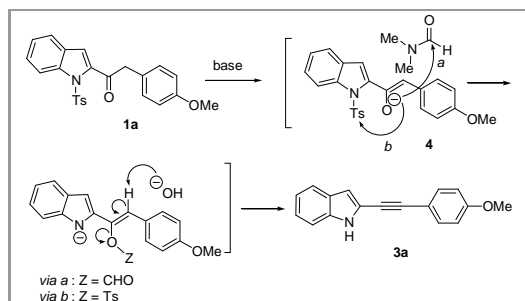
Scheme 1

However, our attempts at the *N*-detosylation of **1a** to obtain the indolyl ketone **2a** using KOH in MeOH–H₂O or in THF–H₂O were unsuccessful: short reaction times only furnished starting material, and stronger conditions, longer reaction times and/or higher temperatures led to degradation.⁴ When the reaction was run in DMF with KOH at 80 °C, an unexpected product was formed. The ¹H-NMR of the product showed the characteristic shifts of 2-indolyl and *p*-methoxyphenyl rings, the absence of the tosyl group, and, surprisingly, the absence of the methylene singlet characteristic of **2a**. The lack of benzylic protons suggested that another transformation had occurred in addition to *N*-deprotection. Moreover, no ketone absorption signal was observed by IR. The mass spectrum (MS = 247) of the purified product indicated loss of one molecule of H₂O and loss of the tosyl group in relation to the starting material **1a**. The aforementioned data, combined with the observation of two quaternary carbons at δ 92.5 and 80.4 ppm in the ¹³C-NMR spectrum of the compound, led us to identify it as 2-(4-methoxyphenylethynyl)-1*H*-indole (**3a**).

A literature search for dehydrations of phenyl benzyl ketones to yield bisarylacetylenes only provided a few examples, all of which shared a common synthetic

pathway: transformation of the ketone into an enol derivative with a good *O*-substituted leaving group, followed by basic elimination to give the bisarylacetylene.⁵ No precedent was found for this type of reaction with *N*-tosyl-2-indolyl ketones as substrate, encouraging us to investigate the scope and limitations of this new route to aryl-heteroaryl-acetylenes⁶, which are versatile synthetic intermediates for the preparation of bioactive natural compounds.⁷

We envisaged transformation of **1a** into **3a** via two possible mechanisms, both of which imply *O*-activation of the enolate **4** followed by elimination, but which differ in their respective leaving groups. Hence enolate **4** could react with DMF to give an enol formiate (Scheme 2, a) that loses both the tosyl group and potassium formiate by KOH. Alternatively, intramolecular *O*-tosylation of **4** to provide indole-deprotection and the enol-leaving group intermediate could also lead to **3** (Scheme 2, b).



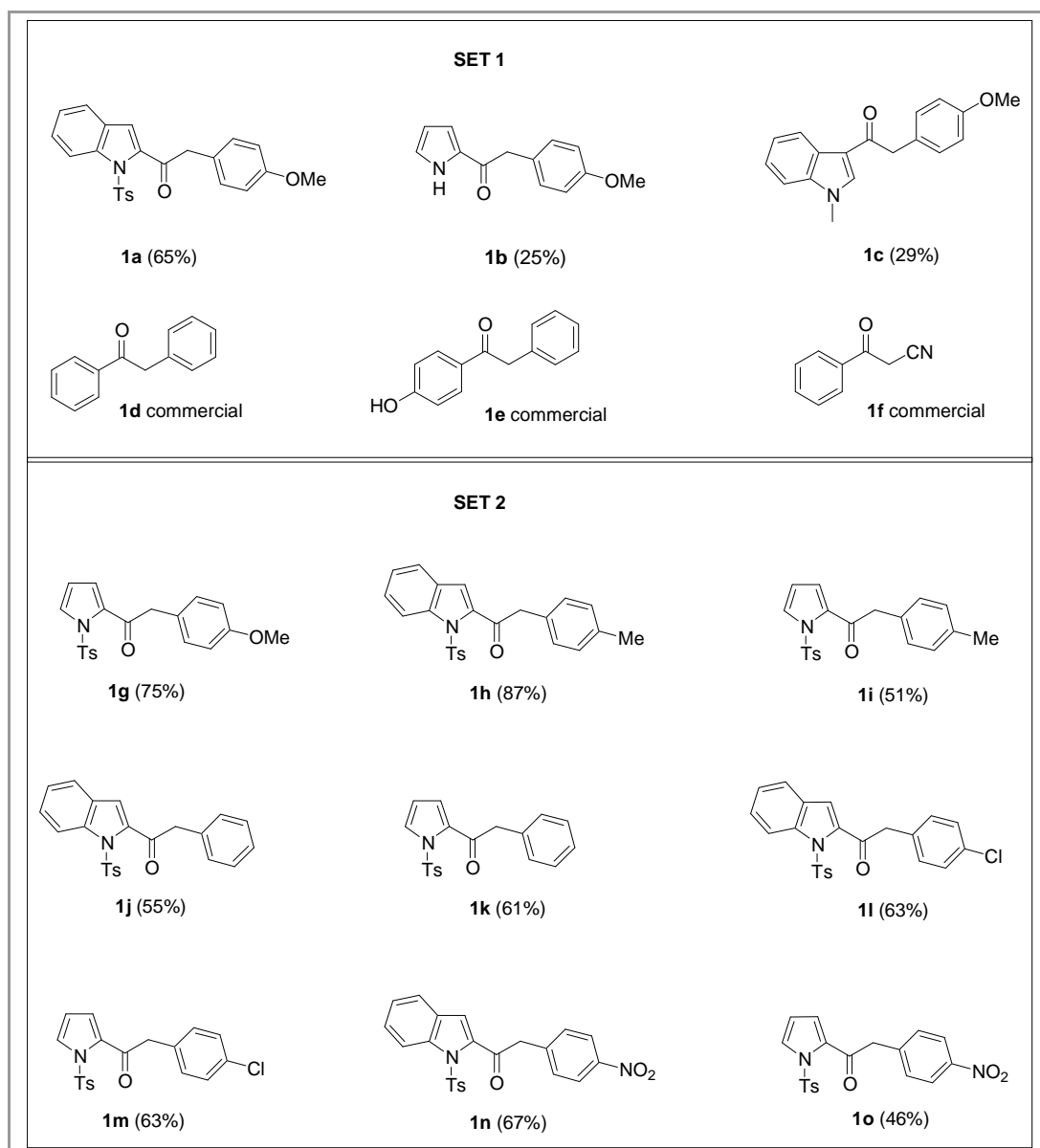
Scheme 2

To discriminate between both mechanisms and investigate the importance of the *N*-tosyl group and/or the reaction solvent, several experiments were carried out using the two sets of ketones shown in Figure 1. The set 1 contains the model (**1a**), heteroaryl benzyl ketones without the tosyl protecting group (**1b** and **1c**), aryl benzyl ketones (**1d** and **1e**), and the aryl ketone **1f**. The set 2 contains the *N*-tosylheteroaryl benzyl ketones **1g-o** that differs in the heterocycle (pyrrole or indole) and in the substituents on the benzyl ring.

The *N*-tosylindolyl ketones **1g-m** were obtained using the same method as that for compound **1a**, indicated in Scheme 1. However, the method did not work for *p*-nitrophenylacetyl chloride. Thus, ketones **1n-o** were synthesized by direct condensation of the 2-lithioheterocycle with the acid chloride. Finally, ketones **1b** and **1c**, with unsubstituted pyrrole and *N*-methylindole, were prepared by direct acylation of the heterocycle using AlCl₃ or Et₂AlCl⁸ as catalysts, the latter of which provided for a more facile work-up.

The results of the study are summarized in Table 1. Ketones **1b-f**, which do not contain an *N*-tosyl group, were treated with KOH in DMF under similar conditions to those used for **1a**. In all cases, the starting material was recovered after 1-3 h of reaction, whereas decomposition compounds (entries 2-6) were obtained with longer reaction times. Compound **1f** was used to test if increasing the acidity of the α -protons favours enolate formation and/or subsequent formylation. Again, the starting material was recovered after 24 h of reaction at 80 °C. These results were the first indication of the importance of the *N*-tosyl group (Scheme 2, b) for the success of the reaction.

Treatment of pyrrolyl ketone **1g** with KOH in DMF afforded pyrrolylacetylene **3g** (entry 7) in only 19% yield, whereas use of a stronger base (NaH) increased the yield to 93% (entry 8). To determine if this stark improvement was general, ketone **1a** was reacted with NaH in DMF. Acetylene **3a** (entry 9) was thus obtained in 82% yield, underscoring the importance of the base. The ketones **1g-o** are *N*-tosylheterocycles that differ in their respective heterocyclic rings and in their phenyl substituents: compounds **1a** and **1g-i** have electron-donating groups, compounds **1l-o** have electron-withdrawing groups, and **1j-k** have unsubstituted phenyl rings. The ketones **1g-m** were reacted with NaH in DMF to give the acetylenes **3g-m** in good to excellent yields (entries 7-15). In contrast, reaction of

**Figure 1**

the ketones **1n** and **1o**, which have the strongest electron-withdrawing substituents, gave the ketones **2n** and **2o**, respectively, and did not lead to any substantial amount of the desired acetylene derivatives (entries 16, 17). Treatment of **1n** and **1o** with KOH in DMF afford-

ed the deprotected ketones **2n** and **2o** in 96% and 58% yield, respectively (entries 18, 19). The results obtained for the *p*-nitrobenzyl ketones could be imputed to the strongly electron-withdrawing nitro group, which decrease the nucleophilicity of the enolate and favours

nucleophilic attack on the sulphonyl group to produce the deprotection.

Table 1 Synthesis of bisaryl acetylenes

$\text{R}^1-\text{C}(=\text{O})-\text{CH}_2-\text{R}^2 \xrightarrow{\text{Base, DMF}} \text{R}^3-\text{C}(=\text{O})-\text{CH}_2-\text{R}^2 \text{ or } \text{R}^3-\text{C}\equiv\text{C}-\text{R}^2$					
Entry	$\text{R}^1-\text{C}(=\text{O})-\text{CH}_2-\text{R}^2$ 1	Base	React. Time ^a	2 R ³ , yield	3 R ³ , yield
1	a	KOH	3 h	----	2-indolyl, 69%
2	b	KOH	3 h	SM ^b	
3	c	KOH	1 h	SM ^b	
4	d	KOH	2 h	SM ^b	
5	e	KOH	2 h	SM ^b	
6	f	KOH	3 h	SM	
7	g	KOH	1 h ^b	----	2-pyrrolyl, 19%
8	g	NaH	1 h	----	2-pyrrolyl, 93%
9	a	NaH	3.5 h	----	2-indolyl, 82%
10	h	NaH	2 h ^b	----	2-indolyl, 47%
11	i	NaH	2 h	----	2-pyrrolyl, 85%
12	j	NaH	1 h ^b	----	2-indolyl, 37%
13	k	NaH	1 h	----	2-pyrrolyl, 74%
14	l	NaH	2.5 h	----	2-indolyl, 93%
15	m	NaH	2 h	----	2-pyrrolyl, 66%
16	n	NaH	4 h	2-indolyl, 28%	----
17	o	NaH	4 h	2-pyrrolyl, 50%	----
18	n	KOH	2 h	2-indolyl, 96%	----
19	o	KOH	2 h	2-pyrrolyl, 58%	----

a: reaction time was determined by monitoring consumption of the starting material by TLC.

b: longer reaction times led to decomposition products.

These results clearly showed the importance of the *N*-tosyl group for acetylene formation. We then assayed the reaction of **1a** with NaH in several solvents to rule out a

mechanism in which the enolate reaction is solvent dependent (Scheme 2, a). Dimethyl sulfoxide (DMSO), *N,N*-dimethylacetamide (DMA), dichloromethane (DCM), *N*-methyl-2-pyrrolidone (NMP), and dimethox-

methane (DME) were thus evaluated as solvents. The experiments were done at 80 °C, and monitored by HPLC⁹ after 3 and 5 h. Only starting material was observed when DCM and DME were used as solvent, but **3a** was produced using DMSO (product isolated in 64% yield), NMP (54%), and DMA (37%) after 5 h of reaction.

Conclusion

In summary, a new procedure for the synthesis of arylethynyl heterocycles has been developed. The procedure comprises heating heteroaryl ketones—readily obtained in good yields—with NaH in DMF. The 1-tosyl-2-heteroaryl ketone general structure is essential for the elimination step, as none of the ketones lacking a tosyl group (**1b-1f**) provided the corresponding acetylenes. The acetylene formation is not solvent-dependent. Notwithstanding, DMF was the highest yielding solvent tested for the formation of acetylene **3a**, followed by DMSO, NMP and DMA.

Reagents and solvents were purified according to *Purification of Laboratory Chemicals*.¹⁰ Melting points (Mp) were determined using a Büchi Melting Point B540 in open capillaries and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer in automatic mode. Multiplicity of the carbons was assigned using DEPT and gHSQC experiments. Multiplicities of ¹³C and ¹H-NMR are indicated with the usual abbreviations according to off-resonance (¹³C-NMR) decoupling: (s) singlet, (d) doublet, (t) triplet, (q) quadruplet, and also, for ¹H-NMR, (m) multiplet and (bs) broad singlet. Spectra were referenced to an appropriate residual solvent peak (CDCl₃). IR spectra were obtained on a Thermo Nicolet FT-IR spectrometer. HRMS were performed on an Agilent LC/MSD-TOF high resolution mass spectrometer using ESI-MS ionization in positive/negative mode by the Mass Spectrometry Service of the University of Barce-

lona. All starting ketones were prepared in our laboratory except **1d-f**, which were purchased from Aldrich.

General procedure for the preparation of the ketones **1a** and **1g-o**. Preparation of *N*-tosyl-2-(4-methoxyphenylacetyl)indole (**1a**)

To a solution of *N*-tosylindole (108 mg, 0.4 mmol) in dry THF (5 mL) at -78 °C, was added BuLi (2.5 M in hexane, 176 µL, 0.4 mmol) dropwise. The solution was stirred for 30 min at low temperature, and then trimethyltin chloride (1 M in THF, 440 µL, 0.4 mmol) was added. The mixture was allowed to reach room temperature. After 2 h, the solution was quenched with sat. aq. KF (5 mL). The organic phase was separated, dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. The tin derivative was then diluted in dry toluene (5 mL) and added to a solution of 4-methoxyphenylacetyl chloride (128 µL, 0.8 mmol) in dry toluene (5 mL). PdCl₂(PPh₃)₂ (28 mg, 0.04 mmol) and CuI (15 mg, 0.08 mmol) were then added, and the mixture was refluxed for 16 h. After cooling, the crude was washed with sat. aq. NaHCO₃ (3 x 20 mL) and brine (20 mL), dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. Purification by flash chromatography on silica gel (95:5 hexane/EtOAc) afforded the ketone **1a** as a yellow solid (115 mg, 65%); mp (MeOH) 117-119 °C.

IR (KBr): 3012, 2896, 1689, 1512, 1245 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.09 (d, *J* = 8.3 Hz, 1 H, H-4), 7.74 (d, *J* = 8.4 Hz, 2 H, Ts), 7.49 (d, *J* = 8.3 Hz, 1 H, H-7), 7.41 (t, *J* = 8.3 Hz, 1 H, H-6), 7.26-7.21 (m, 3 H, H-5, H-2', 6'), 7.15 (d, *J* = 8.4 Hz, 2 H, Ts), 6.97 (s, 1 H, H-3), 6.85 (d, *J* = 8.7 Hz, 2 H, H-3', 5'), 4.23 (s, 2 H, CH₂), 3.76 (s, 3 H, OCH₃), 2.30 (s, 3 H, CH₃).

¹³C-NMR (CDCl₃): δ = 193.1 (s), 158.6 (s), 145.0 (s), 139.4 (s), 138.3 (s), 134.4 (s), 130.7 (d), 129.4 (d), 128.7

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(s), 127.3 (d), 127.2 (d), 126.0 (s), 124.4 (d), 122.6 (d), 116.8 (d), 115.6 (d), 114.0 (d), 55.2 (q), 48.5 (t), 21.5 (q).

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{21}NO_4S$: 420.1191; found: 420.1261.

***N*-Tosyl-2-(4-methoxyphenylacetyl)pyrrole (1g)**

Mp (MeOH) 111-114 °C.

IR (KBr): 3124, 2937, 1720, 1514, 1246 cm^{-1} .

1H -NMR ($CDCl_3$): δ = 7.87 (d, J = 8.2 Hz, 2 H, Ts), 7.78 (dd, J = 3.5 and 1.7 Hz, 1 H, H-5), 7.27 (d, J = 8.2 Hz, 2 H, Ts), 7.07-7.05 (m, 3 H, H-3, H-2',6'), 6.79 (d, J = 8.7 Hz, 2 H, H-3',5'), 6.31 (t, J = 3.5 Hz, 1 H, H-4), 3.90 (s, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3).

^{13}C -NMR ($CDCl_3$): δ = 186.2 (s), 158.5 (s), 144.7 (s), 135.8 (s), 132.9 (s), 130.3 (d), 130.1 (d), 129.3 (d), 128.3 (d), 126.6 (s), 124.0 (d), 114.1 (d), 110.3 (d), 55.2 (q), 45.6 (t), 21.7 (q).

HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{20}H_{19}NO_4S$: 392.1035; found: 392.0927.

***N*-Tosyl-2-(4-tolylacetyl)indole (1h)**

Mp (MeOH) 121-124 °C.

IR (KBr): 2919, 1685, 1362, 1170 cm^{-1} .

1H -NMR ($CDCl_3$): δ = 8.11 (d, J = 8.2 Hz, 1 H, H-4), 7.77 (d, J = 8.8 Hz, 2 H, Ts), 7.50 (d, J = 8.2 Hz, 1 H, H-7), 7.43 (t, J = 8.2 Hz, 1 H, H-6), 7.25 (t, J = 8.2 Hz, 1 H, H-5), 7.20 (d, J = 8.1 Hz, 2 H, H-2',6'), 7.18 (d, J = 8.8 Hz, 2 H, Ts), 7.13 (d, J = 8.1 Hz, 2 H, H-3',5'), 6.98 (s, 1 H, H-3), 4.26 (s, 2 H, CH_2), 2.33 (s, 6 H, 2 CH_3).

^{13}C -NMR ($CDCl_3$): δ = 192.9 (s), 144.9 (s), 139.5 (s), 136.7 (s), 134.6 (s), 131.0 (s), 129.5 (d), 129.5 (s), 129.4 (d), 129.3 (d), 128.7 (s), 127.4 (d), 127.3 (d), 124.4 (d), 122.7 (d), 116.8 (d), 115.7 (d), 49.1 (t), 21.6 (q), 21.1 (q).

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{21}NO_3S$: 404.1242; found: 404.1375.

***N*-Tosyl-2-(4-tolylacetyl)pyrrole (1i)**

IR (KBr): 3149, 2921, 1678, 1143 cm^{-1} .

1H -NMR ($CDCl_3$): δ = 7.87 (d, J = 8.2 Hz, 2 H, Ts), 7.78 (dd, J = 3.4 and 1.7 Hz, 1 H, H-5), 7.28 (d, J = 8.2 Hz, 2 H, Ts), 7.07 (m, 3 H, H-3, H-3',5'), 7.02 (d, J = 8.1 Hz, 2 H, H-2',6'), 6.30 (t, J = 3.4 Hz, 1 H, H-4), 3.92 (s, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3).

^{13}C -NMR ($CDCl_3$): δ = 186.1 (s), 144.7 (s), 136.4 (s), 135.8 (s), 132.9 (s), 131.5 (s), 130.3 (d), 129.3 (d), 129.3 (d), 128.9 (d), 128.3 (d), 124.1 (d), 110.3 (d), 46.1 (t), 21.7 (q), 21.0 (q).

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{19}NO_3S$: 354.1086; found: 354.1168.

***N*-Tosyl-2-(phenylacetyl)indole (1j)**

IR (film): 1686, 1370, 1174 cm^{-1} .

1H -NMR ($CDCl_3$): δ = 8.10 (d, J = 8.2 Hz, 1 H, H-4), 7.75 (d, J = 8.4 Hz, 2 H, Ts), 7.49 (d, J = 8.2 Hz, 1 H, H-7), 7.42 (t, J = 8.2 Hz, 1 H, H-6), 7.31 (d, J = 8.4 Hz, 4 H, H-3',5', and Ts), 7.27-7.23 (m, 2 H, H-5 and H-4'), 7.16 (d, J = 8.4 Hz, 2 H, H-2',6'), 6.98 (s, 1 H, H-3), 4.30 (s, 2 H, CH_2), 2.31 (s, 3 H, CH_3).

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$^{13}\text{C-NMR}$ (CDCl_3): $\delta = 192.7$ (s), 145.0 (s), 139.4 (s), 138.4 (s), 134.5 (s), 134.1 (s), 129.7 (d), 129.4 (d), 128.7 (s), 128.6 (d), 127.4 (d), 127.3 (d), 127.0 (d), 124.4 (d), 122.7 (d), 117.0 (d), 115.7 (d), 49.4 (t), 21.6 (q).

HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_3\text{S}$: 390.1086; found: 390.1157.

N-Tosyl-2-(phenylacetyl)pyrrole (**1k**)

IR (KBr): 3117, 1677, 1350, 1175 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): $\delta = 7.86$ (d, $J = 8.3$ Hz, 2 H, Ts), 7.78 (dd, $J = 3.5$ and 1.7 Hz, 1 H, H-5), 7.27 (d, $J = 8.3$ Hz, 2 H, Ts), 7.25-7.20 (m, 3 H, H-3', 4', 5'), 7.15 (d, $J = 8.2$ Hz, 2 H, H-2', 6'), 7.07 (dd, $J = 3.5$ and 1.7 Hz, 1 H, H-3), 6.30 (t, $J = 3.5$ Hz, 1 H, H-4), 3.96 (s, 2 H, CH_2), 2.40 (s, 3 H, CH_3).

$^{13}\text{C-NMR}$ (CDCl_3): $\delta = 185.8$ (s), 144.7 (s), 135.7 (s), 134.6 (s), 132.9 (s), 130.4 (d), 129.3 (d), 129.1 (d), 128.6 (d), 128.3 (d), 126.8 (d), 124.2 (d), 110.3 (d), 46.4 (t), 21.7 (q).

HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$: 340.0929; found: 340.1003.

N-Tosyl-2-(4-chlorophenylacetyl)indole (**1l**)

Mp (MeOH) 123-126 °C.

IR (KBr): 3050, 2904, 1703, 1370, 1170, 1089 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): $\delta = 8.10$ (d, $J = 8.4$ Hz, 1 H, H-4), 7.72 (d, $J = 8.5$ Hz, 2 H, Ts), 7.50 (d, $J = 8.4$ Hz, 1 H, H-7), 7.43 (t, $J = 8.4$ Hz, 1 H, H-6), 7.30-7.23 (m, 5 H, H-5, H-3', 5', and Ts), 7.16 (d, $J = 8.1$ Hz, 2 H, H-2', 6'), 6.98 (s, 1 H, H-3), 4.27 (s, 2 H, CH_2), 2.31 (s, 3 H, CH_3).

$^{13}\text{C-NMR}$ (CDCl_3): $\delta = 192.4$ (s), 145.1 (s), 139.3 (s), 138.3 (s), 134.2 (s), 133.0 (s), 132.5 (s), 131.1 (d), 129.5 (d), 128.7 (s), 128.7 (d), 127.5 (d), 127.4 (d), 124.5 (d), 122.7 (d), 117.1 (d), 115.7 (d), 48.7 (t), 21.6 (q).

HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{18}\text{ClNO}_3\text{S}$: 424.0696; found: 424.0755.

N-Tosyl-2-(4-chlorophenylacetyl)pyrrole (**1m**)

Mp (MeOH) 116-119 °C.

IR (film): 3141, 2924, 1663, 1437, 675 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): $\delta = 7.85$ (d, $J = 8.3$ Hz, 2 H, Ts), 7.80 (dd, $J = 3.4$ and 1.7 Hz, 1 H, H-5), 7.28 (d, $J = 8.3$ Hz, 2 H, Ts), 7.22 (d, $J = 6.5$ Hz, 2 H, H-3', 5'), 7.06 (m, 3 H, H-3, H-2', 6'), 6.33 (t, $J = 3.4$ Hz, 1 H, H-4), 3.93 (s, 2 H, CH_2), 2.41 (s, 3 H, CH_3).

$^{13}\text{C-NMR}$ (CDCl_3): $\delta = 185.3$ (s), 144.9 (s), 135.6 (s), 132.9 (s), 132.8 (s), 132.7 (s), 130.7 (d), 130.5 (d), 129.3 (d), 128.7 (d), 128.4 (d), 124.1 (d), 110.4 (d), 45.6 (t), 21.7 (q).

HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{16}\text{ClNO}_3\text{S}$: 374.0539; found: 374.0609.

General procedure for the preparation of ketones **1n** and **1o**. Preparation of *N*-Tosyl-2-(4-nitrophenylacetyl)indole (**1n**)

A solution of *N*-tosylindole (444 mg, 1.6 mmol) in dry THF (5 mL) was cooled to -78 °C, and *t*-BuLi (1.7 M in hexane, 1.1 mL, 1.8 mmol) was added dropwise. The reaction mixture was stirred for 30 min, and then 4-nitrophenylacetyl chloride (659 mg, 3.3 mmol) was added dropwise. The solution was allowed to reach room temperature, and stirring was maintained for 3 h. The crude was quenched with sat. aq. NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The organic phase was

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dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. Purification by flash chromatography on silica gel (85:15 hexane/EtOAc) afforded **1n** as a yellow solid (479 mg, 67%); mp (MeOH) 162-167 °C.

IR (KBr): 3077, 2906, 1702, 1522, 1345, 1170 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.19 (d, *J* = 8.8 Hz, 2 H, H-3',5'), 8.10 (d, *J* = 8.4 Hz, 1 H, H-4), 7.70 (d, *J* = 8.3 Hz, 2 H, Ts), 7.51 (m, 1 H, H-7), 7.51 (d, *J* = 8.8 Hz, 2 H, H-2',6'), 7.45 (t, *J* = 8.4 Hz, 1 H, H-6), 7.28 (t, *J* = 8.4 Hz, 1 H, H-5), 7.17 (d, *J* = 8.3 Hz, 2 H, Ts), 7.04 (s, 1 H, H-3), 4.43 (s, 2 H, CH₂), 2.31 (s, 3 H, CH₃).

¹³C-NMR (CDCl₃): δ = 191.6 (s), 147.1 (s), 145.3 (s), 141.5 (s), 139.2 (s), 138.4 (s), 133.8 (s), 130.8 (d), 129.5 (d), 128.8 (s), 127.7 (d), 127.3 (d), 124.8 (d), 123.7 (d), 122.8 (d), 117.5 (d), 115.8 (d), 49.0 (t), 21.6 (q).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₃H₁₈N₂O₅S: 435.0936; found: 435.1000.

***N*-Tosyl-2-(4-nitrophenylacetyl)pyrrole (1o)**

Mp (MeOH) 125-127 °C.

IR (KBr): 3130, 2924, 1681, 1516, 1345, 1171 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.12 (d, *J* = 8.9 Hz, 2 H, H-3',5'), 7.86 (d, *J* = 8.7 Hz, 2 H, Ts), 7.83 (dd, *J* = 3.6 and 1.7 Hz, 1 H, H-5), 7.31 (d, *J* = 8.7 Hz, 2 H, Ts), 7.28 (d, *J* = 8.9 Hz, 2 H, H-2',6'), 7.12 (dd, *J* = 3.6 and 1.7 Hz, 1 H, H-3), 6.36 (t, *J* = 3.6 Hz, 1 H, H-4), 4.09 (s, 2 H, CH₂), 2.41 (s, 3 H, CH₃).

¹³C-NMR (CDCl₃): δ = 184.1 (s), 145.0 (s), 141.8 (s), 135.4 (s), 132.4 (s), 131.0 (d), 130.4 (s), 130.3 (d), 129.4 (d), 128.4 (d), 124.3 (d), 123.7 (d), 110.5 (d), 45.7 (t), 21.7 (q).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₉H₁₆N₂O₅S: 385.0780; found: 385.0851.

1*H*-2-(4-Methoxyphenylacetyl)pyrrole (1b)

Et₂AlCl (1 M in hexane, 11.2 mL, 11.2 mmol) was added to a solution of 4-methoxyphenylacetyl chloride (2.3 mL, 14.9 mmol) in dry DCM (30 mL). The solution was cooled to 0 °C and stirred for 5 min. Pyrrole (517.1 μL, 7.5 mmol) and 2,6-lutidine (1.7 mL, 14.9 mmol) were then added. The solution was allowed to reach room temperature and then stirred for 8 h. The crude reaction was quenched with water (30 mL). The organic phase was separated, and then washed with 2N aq HCl (2 x 20 mL), sat. aq NaHCO₃ (3 x 20 mL) and brine (20 mL). The organic phase was then dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. Purification by flash chromatography on silica gel (94:6 hexane/EtOAc) afforded **1b** as a brown oil (402 mg, 25%).

IR (KBr): 3264, 2933, 1636, 1511, 1248 cm⁻¹.

¹H-NMR (CDCl₃): δ = 9.80 (bs, 1 H, NH), 7.23 (d, *J* = 8.7 Hz, 2 H, H-2',6'), 7.01-6.98 (m, 2 H, H-3 and H-5), 6.86 (d, *J* = 8.7 Hz, 2 H, H-3',5'), 6.28 (td, *J* = 3.7 and 2.51 Hz, 1 H, H-4), 4.00 (s, 2 H, CH₂), 3.78 (s, 3 H, OCH₃).

¹³C-NMR (CDCl₃): δ = 188.2 (s), 158.5 (s), 130.3 (d), 127.1 (s), 125.1 (d), 117.0 (d), 114.0 (d), 110.7 (d), 65.8 (s), 55.2 (q), 44.0 (t).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₃H₁₃NO₂: 216.0946; found: 216.1011.

3-(4-Methoxyphenylacetyl)-*N*-methylindole (1c)

Et₂AlCl (1 M in hexane, 11.6 mL, 11.6 mmol) was added to a solution of 4-methoxyphenylacetyl chloride (2.4 mL, 15.4 mmol) in dry DCM (20 mL). The solution was cooled to 0 °C and stirred for 5 min. *N*-methylindole (1 g, 7.7 mmol) in dry DCM (20 mL) was then added, and the solution was allowed to reach room temperature and

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then stirred for 24 h. The crude reaction was quenched with water (20 mL). The organic phase was separated, and then washed with sat. aq. NaHCO₃ (3 x 15 mL) and brine (15 mL). The organic phase was dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. Purification by flash chromatography on silica gel (80:20 hexane/EtOAc) gave **1c** as a brown solid (624 mg, 29%); mp (MeOH) 101-104 °C.

IR (KBr): 3101, 2933, 1647, 1526, 1249 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.39 (d, *J* = 6.1 Hz, 1 H, H-4), 7.07 (s, 1 H, H-2), 7.30-7.26 (m, 3 H, H-7, H-5, and H-6), 7.23 (d, *J* = 8.7 Hz, 2 H, H-3',5'), 6.83 (d, *J* = 8.7 Hz, 2 H, H-2',6'), 4.05 (s, 2 H, CH₂), 3.78 (s, 3 H, OCH₃), 3.75 (s, 3 H, CH₃).

¹³C-NMR (CDCl₃): δ = 193.1 (s), 158.3 (s), 137.4 (s), 135.7 (d), 130.4 (d), 127.9 (s), 126.6 (s), 123.4 (d), 122.7 (d), 122.6 (d), 116.0 (s), 114.0 (d), 109.5 (d), 55.2 (q), 46.0 (t), 33.5 (q).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₈H₁₇NO₂: 280.1259; found: 280.1320.

General procedure for the arylolethynyl-heterocycles formation. Preparation of 2-(4-methoxyphenylethynyl)-1*H*-indole (**3a**)

NaH (60% in mineral oil, 77 mg, 1.9 mmol) was added to a solution of **1a** (100 mg, 0.2 mmol) in dry DMF (5 mL) at room temperature. The mixture was stirred at 80 °C until the starting material was consumed (monitoring by TLC). Water (3 mL) was added, and the DMF was evaporated under vacuum. The crude was diluted in DCM (10 mL) and water (10 mL), neutralized with 2 N aq. HCl, and then extracted with DCM (3 x 10 mL). The organic layer was dried over anhyd. MgSO₄, filtered, and concentrated under vacuum. Purification by flash chro-

matography on silica gel (96:4 hexane/EtOAc) afforded **3a** as a white solid (49 mg, 82%); mp (MeOH) 163-165 °C.

IR (film): 3419, 2361, 2336, 1028 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.20 (bs, 1 H, NH), 7.60 (d, *J* = 7.6 Hz, 1 H, H-4), 7.50 (d, *J* = 8.8 Hz, 2 H, H-2',6'), 7.35 (d, *J* = 7.6 Hz, 1 H, H-7), 7.22 (t, *J* = 7.6 Hz, 1 H, H-6), 7.18 (t, *J* = 7.6 Hz, 1 H, H-5), 6.90 (d, *J* = 8.8 Hz, 2 H, H-3',5'), 6.80 (s, 1 H, H-3), 3.81 (s, 3 H, OCH₃).

¹³C-NMR (CDCl₃): δ = 159.9 (s), 136.1 (s), 133.0 (d), 127.9 (s), 123.3 (d), 120.7 (d), 120.4 (d), 119.2 (s), 114.6 (s), 114.1 (d), 110.6 (d), 108.3 (d), 92.5 (s), 80.4 (s), 55.3 (q).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₇H₁₃NO: 248.0997; found: 248.1074.

2-(4-Methoxyphenylethynyl)-1*H*-pyrrole (**3g**)

IR (KBr): 3381, 2206, 1900, 1246 cm⁻¹.

¹H-NMR (CDCl₃): δ 8.38 (bs, 1 H, NH), 7.42 (d, *J* = 8.9 Hz, 2 H, H-2',6'), 6.87 (d, *J* = 8.9 Hz, 2 H, H-3',5'), 6.78 (td, *J* = 2.7 and 1.5 Hz, 1 H, H-5), 6.50 (ddd, *J* = 3.6, 2.7, and 1.5 Hz, 1 H, H-3), 6.22 (dd, *J* = 3.6 and 2.7 Hz, 1 H, H-4), 3.82 (s, 3 H, OCH₃).

¹³C-NMR (CDCl₃): δ = 159.5 (s), 132.7 (d), 119.3 (d), 115.3 (s), 114.4 (d), 114.0 (d), 109.3 (d), 90.1 (s), 80.4 (s), 55.3 (q).

HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₃H₁₁NO: 198.0841; found: 198.0916.

2-(4-Tolylolethynyl)-1*H*-indole (**3h**)

Mp (MeOH) 178-182 °C.

IR (KBr): 3398, 2361, 2207 cm⁻¹.

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<p>¹H-NMR (CDCl₃): δ = 8.22 (bs, 1 H, NH), 7.61 (d, J = 8.1 Hz, 1 H, H-4), 7.45 (d, J = 8.0 Hz, 2 H, H-2',6'), 7.33 (d, J = 8.1 Hz, 1 H, H-7), 7.24 (t, J = 8.1 Hz, 1 H, H-6), 7.19 (d, J = 8.0 Hz, 2 H, H-3',5'), 7.14 (t, J = 8.1 Hz, 1 H, H-5), 6.84 (s, 1 H, H-3), 2.39 (s, 3 H, CH₃).</p>	<p>¹H-NMR (CDCl₃): δ = 8.25 (bs, 1 H, NH), 7.62 (d, J = 8.1 Hz, 1 H, H-4), 7.59-7.54 (m, 2 H, H-2',6'), 7.39-7.35 (m, 3 H, H-3',4',5'); 7.34 (d, J = 8.1 Hz, 1 H, H-7), 7.25 (t, J = 8.1 Hz, 1 H, H-6), 7.14 (t, J = 8.1 Hz, 1 H, H-5), 6.85 (s, 1 H, H-3).</p>	Formatted: English (U.K.)
<p>¹³C-NMR (CDCl₃): δ = 138.8 (s), 136.1 (s), 131.3 (d), 129.2 (d), 127.8 (s), 123.4 (d), 120.8 (d), 120.4 (d), 119.5 (s), 119.0 (s), 110.7 (d), 108.5 (d), 92.7 (s), 81.1 (s), 21.5 (q).</p>	<p>¹³C-NMR (CDCl₃): δ = 136.1 (s), 131.4 (d), 128.6 (d), 128.4 (d), 127.8 (s), 123.5 (d), 122.6 (s), 120.8 (d), 120.5 (d), 118.8 (s), 110.7 (d), 108.8 (d), 92.5 (s), 81.8 (s).</p>	Formatted: English (U.K.)
<p>HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₇H₁₃N: 232.1048; found: 232.1118.</p>	<p>HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₆H₁₁N: 218.0891; found: 218.0960.</p>	
<p>2-(4-Tolylethynyl)-1H-pyrrole (3i)</p>	<p>2-(Phenylethynyl)-1H-pyrrole (3k)</p>	
<p>Mp (MeOH) 88-90 °C.</p>	<p>IR (film): 3425, 2204 cm⁻¹.</p>	
<p>IR (KBr): 3432, 2207, 1915 cm⁻¹.</p>	<p>¹H-NMR (CDCl₃): δ = 8.40 (bs, 1 H, NH), 7.48 (m, 2 H, H-2',6'), 7.33 (m, 3 H, H-3',4',5'), 6.80 (td, J = 2.7 and 1.5 Hz, 1 H, H-5), 6.55 (ddd, J = 3.7, 2.7, and 1.5 Hz, 1 H, H-3), 6.23 (dd, J = 3.7 and 2.7 Hz, 1 H, H-4).</p>	Formatted: English (U.K.)
<p>¹H-NMR (CDCl₃): δ = 8.33 (bs, 1 H, NH), 7.37 (d, J = 8.0 Hz, 2 H, H-2',6'), 7.12 (d, J = 8.0 Hz, 2 H, H-3',5'), 6.74 (td, J = 2.6 and 1.6 Hz, 1 H, H-5), 6.51 (ddd, J = 3.6, 2.6, and 1.6 Hz, 1 H, H-3), 6.20 (dd, J = 3.6 and 2.6 Hz, 1 H, H-4), 2.34 (s, 3 H, CH₃).</p>	<p>¹³C-NMR (CDCl₃): δ = 131.2 (s), 131.1 (d), 128.3 (d), 128.0 (d), 123.2 (s), 119.6 (d), 114.9 (d), 109.5 (d), 90.3 (s), 81.8 (s).</p>	Formatted: English (U.K.)
<p>¹³C-NMR (CDCl₃): δ = 138.1 (s), 131.1 (d), 129.1 (d), 120.1 (s), 119.4 (d), 114.6 (d), 113.1 (s), 109.3 (d), 90.4 (s), 81.1 (s), 21.4 (q).</p>	<p>HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₂H₉N: 168.0735; found: 168.0800.</p>	
<p>2-(4-Chlorophenylethynyl)-1H-indole (3l)</p>	<p>2-(4-Chlorophenylethynyl)-1H-indole (3l)</p>	
<p>Mp (MeOH) 178-181 °C.</p>	<p>IR (KBr): 3395, 2209, 825 cm⁻¹.</p>	Formatted: English (U.K.)
<p>HRMS (ESI-TOF): m/z [M + H]⁺ calc for C₁₃H₁₁N: 182.0891; found: 182.0960.</p>	<p>¹H-NMR (CDCl₃): δ = 8.23 (bs, 1 H, NH), 7.61 (d, 1 H, J = 8.1 Hz, H-4), 7.47 (d, 2 H, J = 8.6 Hz, H-2',6'), 7.35 (m, 3 H, H-7, H-3', 5'), 7.25 (t, 1 H, J = 8.1 Hz, H-6), 7.14 (t, 1 H, J = 8.1 Hz, H-5), 6.85 (s, 1 H, H-3).</p>	Formatted: English (U.K.)
<p>2-(Phenylethynyl)-1H-indole (3j)</p>	<p>Mp (MeOH) 149-152 °C.</p>	
<p>IR (KBr): 3385, 2211, 1888 cm⁻¹.</p>	<p>¹³C-NMR (CDCl₃): δ = 136.2 (s), 134.6 (s), 132.6 (d), 128.8 (d), 127.7 (s), 123.7 (d), 121.1 (s), 120.9 (d), 120.6 (d), 118.4 (s), 110.7 (d), 109.2 (d), 91.5 (s), 82.7 (s).</p>	Formatted: English (U.K.)

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₆H₁₀ClN: Mp (MeOH) 155-157 °C.

252.0502; found: 252.0574.

2-(4-Chlorophenylethynyl)-1H-pyrrole (3m)

Mp (MeOH) 100-102 °C.

IR (KBr): 3405, 2201, 802 cm⁻¹.

¹H-NMR (CDCl₃): δ = 8.40 (bs, 1 H, NH), 7.40 (d, 2 H, *J* = 8.6 Hz, H-2',6'), 7.30 (d, 2 H, *J* = 8.6 Hz, H-3',5'), 6.81 (td, 1 H, *J* = 2.6 and 1.5 Hz, H-5), 6.55 (ddd, 1 H, *J* = 3.6, 2.6, and 1.5 Hz, H-3), 6.23 (dd, 1 H, *J* = 3.6 and 2.6 Hz, H-4).

¹³C-NMR (CDCl₃): δ = 145.7 (s), 133.9 (s), 132.3 (d), 128.7 (d), 121.7 (s), 119.8 (d), 115.2 (d), 109.6 (d), 89.4 (s), 82.9 (s).

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₂H₈ClN: 202.0345; found: 202.0386.

2-(4-Nitrophenylacetyl)-1H-indole (2n)

Mp (MeOH) 168-171 °C.

IR (KBr): 3310, 1691, 1652, 1514, 1343 cm⁻¹.

¹H-NMR (CDCl₃): δ = 9.06 (bs, 1 H, NH), 8.21 (d, 2 H, *J* = 8.8 Hz, H-3',5'), 7.74 (d, 1 H, *J* = 8.1 Hz, H-4), 7.52 (d, 2 H, *J* = 8.8 Hz, H-2',6'), 7.39 (m, 2 H, H-7 and H-6), 7.32 (s, 1 H, H-3), 7.18 (t, 1 H, *J* = 8.1 Hz, H-5), 4.36 (s, 2 H, CH₂).

¹³C-NMR (CDCl₃): δ = 188.4 (s), 141.9 (s), 137.6 (s), 134.3 (s), 130.5 (d), 129.5 (s), 127.5 (s), 127.0 (d), 123.8 (d), 123.2 (d), 121.4 (d), 112.2 (d), 110.4 (d), 44.6 (t).

HRMS (ESI-TOF): m/z [M + H]⁺ calc for C₁₆H₁₂N₂O₃: 281.0848; found: 281.0925.

2-(4-Nitrophenylacetyl)-1H-pyrrole (2o)

IR (KBr): 3275, 1642, 1518 cm⁻¹.

¹H-NMR (CDCl₃): δ = 9.57 (bs, 1 H, NH), 8.18 (d, 2 H, *J* = 8.8 Hz, H-3',5'), 7.47 (d, 2 H, *J* = 8.8 Hz, H-2',6'), 7.07 (ddd, 1 H, *J* = 3.9, 2.6, and 1.3 Hz, H-5), 7.03 (ddd, 1 H, *J* = 3.9, 2.6, and 1.3 Hz, H-3), 6.33 (td, 1 H, *J* = 3.9 and 2.6 Hz, H-4), 4.18 (s, 2 H, CH₂).

¹³C-NMR (CDCl₃): δ = 185.8 (s), 147.0 (s), 142.5 (s), 131.2 (s), 130.4 (d), 125.8 (d), 123.7 (d), 117.3 (d), 111.2 (d), 44.3 (t).

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₁₂H₁₀N₂O₃: 231.0691; found: 231.0765.

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Novel Synthesis of Bisaryl Acetylenes