HETEROCYCLES, Vol. 82, No. 2, 2011, pp. 1617 - 1631. © The Japan Institute of Heterocyclic Chemistry
Received, 16th September, 2010, Accepted, 5th November, 2010, Published online, 18th November, 2010
DOI: 10.3987/COM-10-S(E)125

SYNTHESIS OF 2- AND 3-INDOLYLPYRROLES *VIA* 1,3-DIPOLAR CYCLOADDITIONS OF MÜNCHNONES AND NITROALKENES †

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Abstract – A series of 2- and 3-indolylpyrroles were generated *via* 1,3-dipolar cycloadditions between (2-nitrovinyl)indoles and symmetrical and unsymmetrical 1,3-oxazolium-5-olates (münchnones).

INTRODUCTION

Methods for the synthesis of biheteroaryl compounds are of great importance due to the broad applicability and privileged nature[1] of these structures, which include natural products,[2] pharmaceuticals,[3] and materials such as polymers[4] and dyes.[5] Naturally occurring biheteroaryl structures exist as unfused[2] or fused systems, examples of which are shown in **Figure 1**.[2]

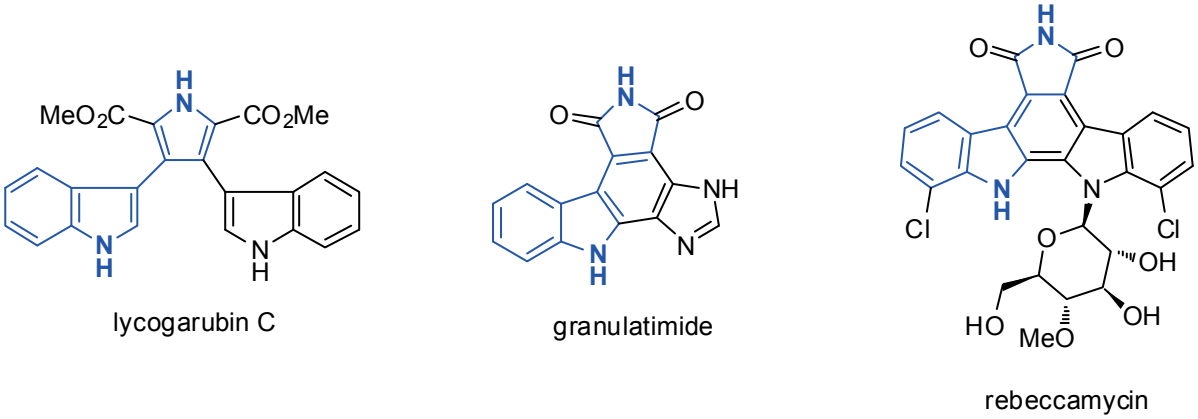


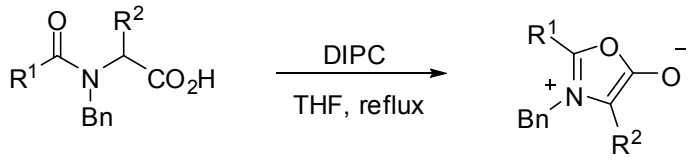
Figure 1. Indolylpyrrole-based Natural Products

† Dedicated to Professor Albert Eschenmoser in celebration of his 85th birthday and his many outstanding contributions to synthetic organic chemistry.

Currently, the most common way to synthesize these heterocycles is with transition metal catalyzed cross-coupling.[6] While these methods are rapidly improving, the direct cross-coupling of two heteroaryl moieties remains a challenge.[7] Few other methods exist for providing convenient access to simple unfused indolylpyrrole core structures. Mohanakrishnan and coworkers recently disclosed a cycloaddition method based on tosylmethylisocyanide (TosMIC) which allows access to protected indolylpyrrole structures.[8] Our laboratory has long been interested in the use of 1,3-oxazolium-5-olates (münchnones) for the synthesis of both fused heteroaromatics[9] and caged systems.[10] The 1,3-dipolar cycloaddition of münchnones and nitroalkenes provides an orthogonal and transition metal-free methodology that allows flexible access to these structures. As an extension of our work with 2- and 3-nitroindoles,[9] we endeavored to examine various 2- and 3-(2-nitrovinyl)indoles as substrates for 1,3-dipolar cycloadditions with symmetrical and unsymmetrical münchnones.

RESULTS AND DISCUSSION

The münchnone precursors were prepared as previously reported[9] and the cyclized münchnones were generated *in situ* (**Scheme 1**) with *N*,*N'*-diisopropylcarbodiimide (DIPC).

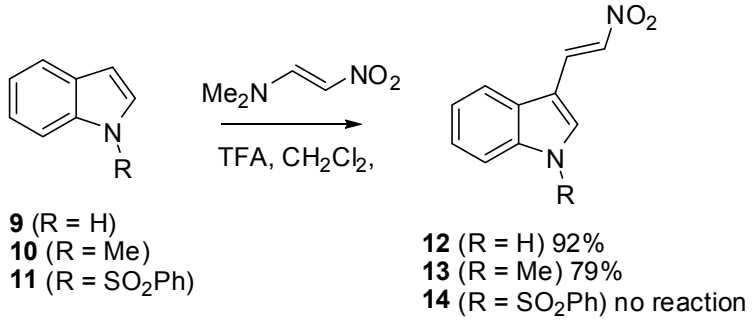


1 ($R^1 = R^2 = Ph$)
2 ($R^1 = R^2 = Me$)
3 ($R^1 = Ph$, $R^2 = Me$)
4 ($R^1 = Me$, $R^2 = Ph$)

5 ($R^1 = R^2 = Ph$)
6 ($R^1 = R^2 = Me$)
7 ($R^1 = Ph$, $R^2 = Me$)
8 ($R^1 = Me$, $R^2 = Ph$)

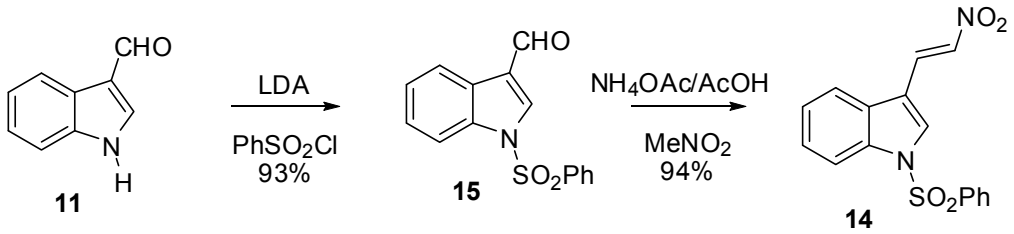
Scheme 1. Generation of Münchnones **5-8**

In lieu of the conventional Henry reaction approach, 3-(2-nitrovinyl)indoles **12** and **13** were synthesized directly from indoles **9** and **10** by an addition-elimination reaction of 1-(dimethylamino)-2-nitroethylene[11] (**Scheme 2**). However, the attempted synthesis of **14** using this route failed, presumably because 1-(phenylsulfonyl)indole **11** is too electron-deficient to undergo the requisite initial Michael addition reaction.



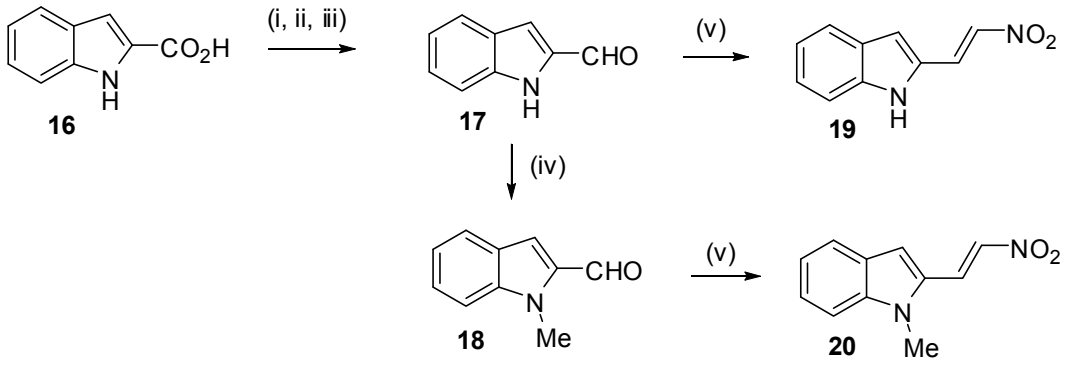
Scheme 2. Synthesis of 3-(2-nitrovinyl)indoles

Compound **14** was instead prepared by *N*-protection of indole-3-carboxaldehyde[12] followed by condensation with nitromethane in a standard Henry reaction[13] (**Scheme 3**).



Scheme 3. Synthesis of 3-(2-nitrovinyl)-1-(phenylsulfonyl)indole

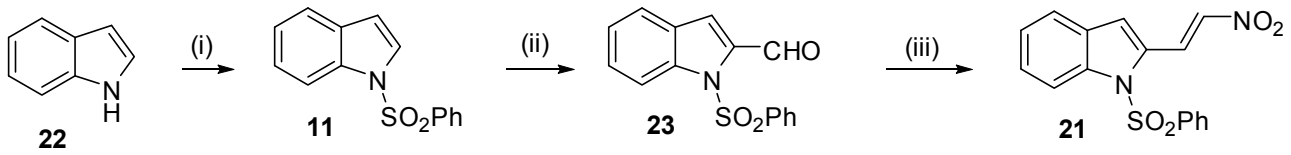
The unprotected and methyl–protected 2-(2-nitrovinyl)indoles were generated in four and five steps, respectively, from commercially available indole-2-carboxylic acid through a sequence of esterification,[14] reduction,[15] oxidation,[15] protection[16] (for the *N*-methyl derivative), and condensation with nitromethane[17] (**Scheme 4**). Attempted generation of **20** from **19** with methyl iodide or dimethyl sulfate did not yield an appreciable amount of the desired product.



(i) H_2SO_4, MeOH; (ii) DIBAL-H, THF; (iii) MnO_2, MeCN, 94% over three steps; (iv) Aliquat 336, dimethyl sulfate, 50% aq. NaOH, CH_2Cl_2, 98%; (v) a) 50% aq. NaOH, $MeNO_2$, MeOH, b) 20% aq. HCl (**19**, 87%; **20**, 84%)

Scheme 4. Synthesis of 2-(2-nitrovinyl)indoles from indole-2-carboxylic acid

Instead, 1-(phenylsulfonyl)indole derivative **21** was generated (**Scheme 5**) from indole *via* *N*-protection,[18] C2-lithiation (quenching with DMF),[19] and condensation with nitromethane.[17]

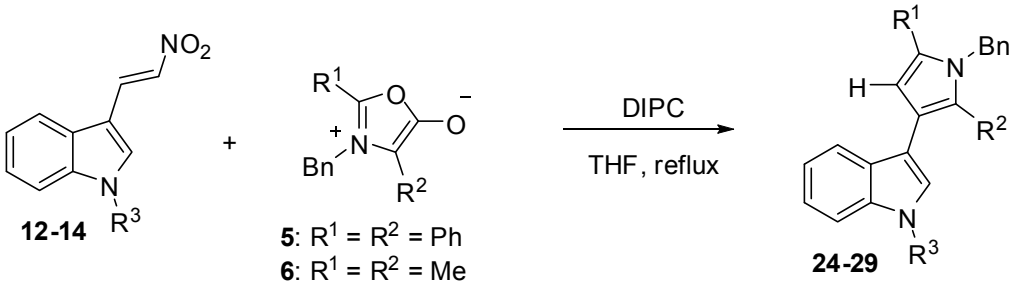


(i) $PhSO_2Cl$, NaOH, *n*-Bu_4NHSO_4, CH_2Cl_2, 97%; (ii) a) *n*-BuLi, THF, b) DMF, 69%; (iii) a) 50% aq. NaOH, $MeNO_2$, MeOH, b) 20% aq. HCl, 87%

Scheme 5. Synthesis of 2-(2-nitrovinyl)-1-(phenylsulfonyl)indole

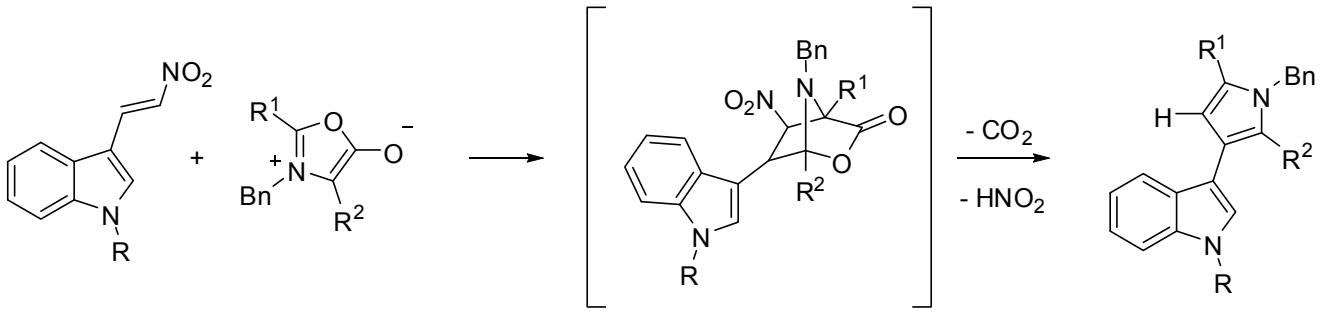
With the nitroalkenes in hand, their reactivity with münchnones **5-8** was investigated. Gratifyingly, 3-(2-nitrovinyl)indoles **12-14** reacted smoothly with symmetrical münchnones **5** and **6** to give the corresponding pyrrole products **24-29** in good yields (**Table 1**). It is proposed that the 1,3-dipolar cycloadditions proceed though a bicyclic adduct which expels carbon dioxide and eliminates nitrous acid to give the substituted *N*-benzyl-3-indolylpyrroles (**Scheme 6**).[9] The protecting group on the indole (or lack thereof) seemingly had no effect on the reaction.

Table 1. Reaction of 3-Nitroalkenes with Symmetrical Münchnones.



Indole	Münchnone	R^3	Product	Yield[a]
12	**5**	H	**24**	78%
13	**5**	Me	**25**	62%
14	**5**	SO_2Ph	**26**	81%
12	**6**	H	**27**	84%
13	**6**	Me	**28**	75%
14	**6**	SO_2Ph	**29**	68%

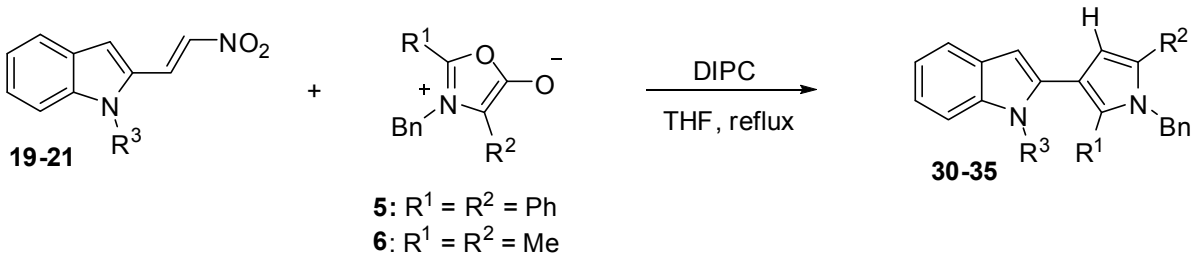
[a]Yield refers to isolated products after column chromatography.



Scheme 6. Proposed Course of 1,3-Dipolar Cycloadditions

In a similar manner, 2-(2-nitrovinyl)indoles **19-21** were allowed to react with symmetrical münchnones **5** and **6**. The corresponding 3-pyrrol-2-ylindoles were obtained in high yield and again, the various protecting groups on the starting indoles had no effect on the outcome of the reaction (**Table 2**).

Table 2. Reaction of 2-Nitroalkenes with Symmetrical Münchnones.



19-21

5: $R^1 = R^2 = Ph$
6: $R^1 = R^2 = Me$

30-35

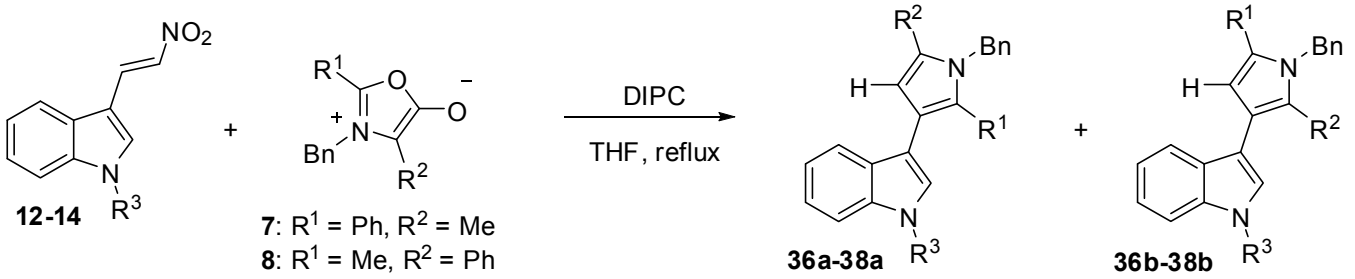
Indole	Münchnone	R^3	Product	Yield[a]
19	**5**	H	**30**	92%
20	**5**	Me	**31**	90%
21	**5**	SO_2Ph	**32**	94%
19	**6**	H	**33**	92%
20	**6**	Me	**34**	70%
21	**6**	SO_2Ph	**35**	86%

[a]Yield refers to isolated products after column chromatography.

With the success of münchnones **5** and **6**, we turned our attention to unsymmetrical münchnones **7** and **8** and tested them under the same reaction conditions. The reaction of münchnone **7** with 3-(2-nitrovinyl)indoles **12-14** gave the expected pyrrole products in moderate to good yield with reasonably good regioselectivity (**Table 3**). The protecting group on the indole nitrogen did appear to

alter the reaction; phenylsulfonyl deriviative **14** was optimal and yielded the major product in an 88:12 ratio and in 71% overall yield. However, münchnone **8** gave substantially different results (**Table 3**). In each case, **8** was both less reactive (lower yielding) and less regioselective. Phenylsulfonyl deriviative **14** still provided the highest yielding reaction (65%) but was completely nonselective, giving essentially a 1:1 mixture of isomers.

Table 3. 3-Nitroalkenes with Unsymmetrical Münchnones



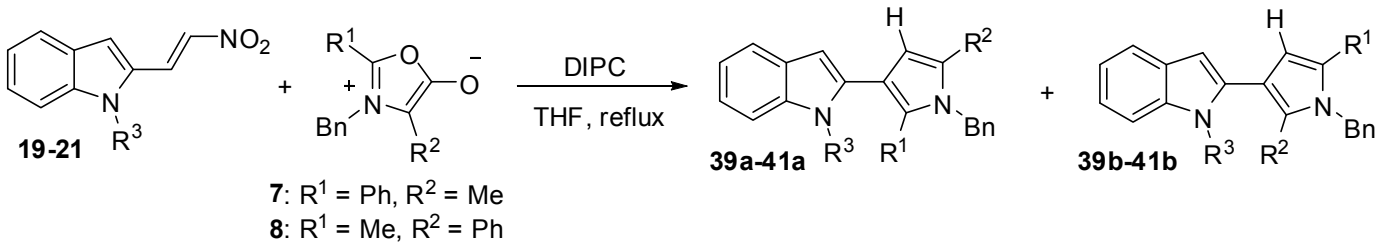
12-14 + **7**: R^1 = Ph, R^2 = Me; **8**: R^1 = Me, R^2 = Ph → **36a-38a** + **36b-38b**

Indole	Münchnone	R^3	Products	Ratio (a:b)[a]	Yield[b]
12	**7**	H	**36a : 36b**	77 : 23	51%
13	**7**	Me	**37a : 37b**	74 : 26	86%
14	**7**	SO_2Ph	**38a : 38b**	88 : 12	71%
12	**8**	H	**36a : 36b**	37 : 63	20%
13	**8**	Me	**37a : 37b**	44 : 56	39%
14	**8**	SO_2Ph	**38a : 38b**	49 : 51	65%

[a]Regiochemistry was determined by NOE interactions of the pyrrole ring proton with either the methyl or phenyl group of the pyrrole.
[b]Yield refers to isolated products after column chromatography.

Once again, 2-(2-nitrovinyl)indoles **19-21** proved more reactive then their isomeric counterparts. The reactions with münchnone **7** proceeded in good to excellent yield with good regioselectivity (**Table 4**). While phenylsulfonyl indole **21** gave the best yield, it also showed the lowest selectivity of the group. Methyl–protected indole **20** exhibited a 9:1 selectivity with a 76% yield. As expected, münchnone **8** was less reactive in all cases; however, the selectivity was reasonably good in each case. Most surprisingly, *N*-methylindole **20** afforded the opposite major product then what was expected based on the other results in this study. The reason for this change is unknown and currently under investigation. As has mostly been the case, *N*-phenylsulfonylindole **21** gave optimal results with a ratio of 91:9 in 78% yield.

Table 4. 2-Nitroalkenes with Unsymmetrical Münchnones



Indole	Münchnone	R^3	Products	Ratio (a:b)[a]	Yield[b]
19	**7**	H	**39a : 39b**	87 : 13	89%
20	**7**	Me	**40a : 40b**	90 : 10	76%
21	**7**	SO_2Ph	**41a : 41b**	79 : 21	95%
19	**8**	H	**39a : 39b**	26 : 74	62%
20	**8**	Me	**40a : 40b**	70 : 30	45%
21	**8**	SO_2Ph	**41a : 41b**	9 : 91	78%

[a]Regiochemistry was determined by NOE interactions of the pyrrole ring proton with either the methyl or phenyl group of the pyrrole.
[b]Yield refers to isolated products after column chromatography.

In summary, we report a reaction protocol that allows access to a variety of substituted 2- and 3-indolyl pyrroles in moderate to high yields. In the case of unsymmetrical münchnones, the regioselectivity varies substantially from being completely nonselective to where the major products are obtained in a 9:1 ratio. Extensions of this methodology to other heterocyclic systems as well as mechanistic and computational studies designed to rationalize both the reactivity and regioselectivity are currently underway and will be reported in due course.

EXPERIMENTAL

General: ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and NOE experiments were performed on a Varian Unity spectrometer. Chemical shifts are reported in ppm with the solvent signal used as an internal reference ($CDCl_3$, 7.26 ppm). Coupling constants are reported in Hz and peak splittings are listed as broad singlet (br s), singlet (s), doublet (d), doublet of doublets (dd), triplet (t), or multiplet (m). Tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl immediately prior to use. All other commercial reagents were used as received.

3-(2-Nitrovinyl)-*1H*-indole[11] **(12):** A round bottom flask was charged with 1-(dimethylamino)-2-nitroethylene (1.06 g, 9.1 mmol, 1.2 eq.) and CH_2Cl_2 (25 mL). The flask was cooled

to 0 °C. Trifluoroacetic acid (2.02 g, 17.7 mmol, 2.3 eq.) was added slowly, followed by a solution of indole (2.00 g, 7.6 mmol, 1.0 eq.) in CH_2Cl_2 (15 mL). The resulting solution was stirred at 0 °C for 65 min then poured into ice water (100 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 60 mL), brine (1 x 60 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **12** as a light brown solid (1.32 g, 92%). ^{1}H NMR ($CDCl_3$) δ 8.74 (br s, 1H), 8.30 (d, 1H, J = 13.4 Hz), 7.83-7.78 (m, 2H), 7.68 (d, 1H, J = 2.9 Hz), 7.50-7.46 (m, 1H), 7.39-7.32 (m, 2H).

1-Methyl-3-(2-nitrovinyl)-1*H*-indole[11] **(13):** A round bottom flask was charged with 1-(dimethylamino)-2-nitroethylene (2.12 g, 18.2 mmol, 1.2 eq.) and CH_2Cl_2 (50 mL). The flask was cooled to 0 °C. Trifluoroacetic acid (4.04 g, 35.4 mmol, 2.3 eq.) was added slowly, followed by a solution of 1-methylindole (2.00 g, 15.2 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL). The resulting solution was stirred at 0 °C for 45 min then poured into ice water (150 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 100 mL), brine (1 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **13** as an orange solid (2.43 g, 79%). ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1H, J = 13.4 Hz), 7.78-7.73 (m, 2H), 7.52 (s, 1H), 7.42-7.31 (m, 3H), 3.87 (s, 3H).

3-(2-Nitrovinyl)-1-(phenylsulfonyl)-1*H*-indole[20] **(14):** A round bottom flask was charged with ammonium acetate (2.14 g, 27.8 mmol, 2.4 eq.), nitromethane (4.87 g, 79.8 mmol, 6.9 eq.), and acetic acid (25 mL). 1-(phenylsulfonyl)indole-3-carboxaldehyde (3.30 g, 11.6 mmol, 1 eq.) was added and the mixture was heated to 100 °C for 6 h, cooled to room temperature, and stirred overnight. The reaction mixture was poured into distilled water (100 mL) and 2M NaOH was added with stirring until the pH = 7. The aqueous solution was extracted with EtOAc (4 x 50 mL); the combined organic extracts were washed with brine (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **14** as a tan solid (3.58 g, 94%). ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.05-7.94 (m, 2H), 7.77-7.37 (m, 9H).

Representative procedure for the synthesis of 19-21: A round bottom flask was charged with indole-2-carboxaldehyde (1.0 g, 6.89 mmol, 1.0 eq.), nitromethane (1.5 g, 24.6 mmol, 3.6 eq), and methanol (25 mL). The flask was cooled to 0 °C (ice bath) and 50% aqueous sodium hydroxide (7.5 mL) was added slowly dropwise with vigorous stirring. After 90 min, an ice-water mixture (25 mL) was

added. The resulting mixture was poured slowly into ice cold 20% aqueous HCl (150 mL) under stirring. After 5 min, the crude **19** which precipitated was collected by vacuum filtration over sintered glass and dried in air.

2-(2-Nitrovinyl)-1*H*-indole[17] **(19):** The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **19** as a light brown solid (1.13 g, 87%). ^{1}H NMR ($CDCl_3$) δ 8.31 (br s, 1H), 8.05 (d, 1H, J = 13.4 Hz), 7.66 (d, 1H, J = 8.1 Hz), 7.50 (d, 1H, J = 13.7 Hz), 7.42-7.32 (m, 2H), 7.20-7.15 (m, 1H), 7.07 (s, 1H).

1-Methyl-2-(2-nitrovinyl)-1*H*-indole[21] **(20):** The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **20** as an orange solid (1.17 g, 84%). ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 1H, J = 13.4 Hz), 7.71-7.63 (m, 2H), 7.35 (d, 2H, J = 5.6 Hz), 7.19-7.13 (m, 1H), 7.10 (s, 1H), 3.88 (s, 3H).

2-(2-Nitrovinyl)-1-(phenylsulfonyl)-1*H*-indole (21): The crude product was purified by flash chromatography over silica gel (30% EtOAc in hexanes) to give **21** as a yellow solid (0.91 g, 87%). ^{1}H NMR ($CDCl_3$) δ 8.81 (d, 1H, J = 13.4 Hz), 8.26 (d, 1H, J = 8.6 Hz), 7.76 (d, 1H, J = 9.5 Hz), 7.59-7.26 (m, 8H), 7.11 (s, 1H); HRMS (ESI^+) m/z calculated for $C_{16}H_{13}N_2O_4S$ (MH^+) 329.0596, found 329.0602.

Representative procedure for the reaction of nitroalkenes and münchnones (24-41): A round bottom flask was charged with the 3-(2-nitrovinyl)indole (94 mg, 0.50 mmol, 1 eq.), münchnone precursor **1** (518 mg, 1.5 mmol, 3 eq.) and THF (20 mL). DIPC (233 μL, 1.5 mmol, 3 eq.) was added and the mixture was heated to reflux under nitrogen for 18-24 h. Once TLC indicated complete consumption of the nitroalkene, the mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified directly by flash chromatography over silica gel (1:3 CH_2Cl_2:hexanes) to yield pure **24**.

3-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1*H*-indole (24): White solid, 78% yield; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2H, J = 7.1 Hz), 7.52-7.11 (m, 16H), 6.81 (s, 1H), 6.76 (d, 2H, J = 7.6 Hz), 6.70 (s, 1H), 5.20 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 139.7, 136.2, 135.7, 133.9, 133.8, 132.3, 132.1, 131.6, 131.1, 129.3, 129.1, 129.0, 128.9, 128.7, 128.5, 128.5, 128.0, 127.6, 127.2, 127.0, 126.3, 122.0, 120.6, 119.7, 117.0, 112.2, 111.2, 110.4, 48.8; HRMS (ESI^+) m/z calculated for $C_{31}H_{25}N_2$ (MH^+) 425.2018, found 425.2026.

3-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (25): White solid, 62% yield; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 1H, J = 7.8 Hz), 7.48 (d, 2H, J = 6.8 Hz), 7.38-7.06 (m, 15H), 6.75-6.72 (m, 3H), 6.57

(s, 1H), 5.18 (s, 2H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.7, 137.0, 135.6, 134.0, 133.8, 132.1, 131.5, 129.3, 128.6, 128.4, 128.4, 127.7, 127.5, 127.2, 126.9, 126.7, 126.3, 121.5, 120.8, 119.1, 110.7, 110.5, 109.2, 74.0, 48.8, 32.9; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2$ (MH^+) 439.2174, found 439.2172.

3-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (26): Light orange solid, 81% yield; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H, J = 8.3 Hz), 7.78 (d, 1H, J = 7.8 Hz), 7.67 (d, 2H, J = 7.8 Hz), 7.52-7.17 (m, 18H), 7.13 (s, 1H), 6.77-6.74 (m, 3H), 5.22 (s, 2H), ^{13}C NMR ($CDCl_3$) δ 139.3, 138.3, 136.0, 135.4, 133.7, 133.5, 132.9, 131.4, 131.2, 129.4, 129.3, 128.8, 128.7, 128.6, 127.9, 127.4, 127.2, 124.8, 123.5, 123.0, 121.3, 118.9, 114.5, 113.9, 110.1, 48.9; HRMS (ESI^+) m/z calculated for $C_{37}H_{29}N_2O_2S$ (MH^+) 565.1950, found 565.1942.

3-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)- 1*H*-indole (27): Light yellow solid, 84% yield; ^{1}H NMR ($CDCl_3$) δ 8.07 (br s, 1H), 7.80 (d, 1H, J = 7.8 Hz), 7.41-7.14 (m, 7H), 7.00 (d, 2H, J = 7.6 Hz), 6.23 (s, 1H), 5.13 (s, 2H), 2.26 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.9, 136.4, 129.0, 127.7, 127.3, 126.0, 122.1, 121.6, 120.7, 119.6, 113.5, 113.3, 111.2, 107.6, 47.3, 12.6, 11.4; HRMS (ESI^+) m/z calculated for $C_{21}H_{21}N_2$ (MH^+) 301.1705, found 301.1703.

3-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (28): Yellow solid, 75% yield; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 1H, J = 7.8 Hz), 7.39-7.26 (m, 5H), 7.18 (t, 1H, J = 6.8 Hz), 7.15-7.01 (m, 3H) 6.24 (s, 1H), 5.15 (s, 2H)3.84 (s, 3H), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.1, 129.0, 128.1, 127.6, 127.3, 126.4, 126.0, 124.5, 121.7, 120.9, 119.1, 113.4, 112.0, 109.3, 107.6, 47.3, 33.0, 12.6, 11.5; HRMS (ESI^+) m/z calculated for $C_{22}H_{23}N_2$ (MH^+) 315.1861, found 315.1856.

3-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (29): Orange solid, 68% yield; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 8.3 Hz), 7.96-7.90 (m, 3H), 7.74 (d, 2H, J = 7.8 Hz), 7.54-7.25 (m, 6H), 6.98 (d, 2H, J = 8.0 Hz), 6.19 (s, 1H), 5.12 (s, 2H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.4, 138.3, 135.6, 133.9, 131.6, 129.4, 129.1, 128.4, 127.7, 127.0, 125.9, 125.4, 123.5, 122.2, 121.4, 120.0, 113.9, 111.0, 107.1, 47.3, 12.6, 11.4; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2O_2S$ (MH^+) 441.1637, found 441.1631.

2-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1*H*-indole (30): White solid, 92% yield; ^{1}H NMR ($CDCl_3$) δ 7.73 (br s, 1H), 7.56-7.36 (m, 11H), 7.20-7.07 (m, 6H), 6.77-6.75 (m, 3H), 6.47 (s, 1H), 5.12 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 139.1, 136.3, 136.0, 134.7, 133.3, 132.9, 131.9, 131.6, 129.4, 129.3, 129.1, 129.0, 128.8, 128.6, 127.8, 127.2, 126.2, 121.2, 120.0, 119.9, 115.6, 110.5, 108.3, 98.7, 48.7; HRMS (ESI^+) m/z

calculated for $C_{31}H_{25}N_2$ (MH^+) 425.2018, found 425.2018.

2-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (31): Pale yellow solid, 90% yield; ^{1}H NMR ($CDCl_3$) δ 7.53-7.03 (m, 17H), 6.72 (d, 2H, J = 7.8 Hz), 6.49 (s, 1H), 6.34 (s, 1H), 5.23 (s, 2H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.2, 132.0, 130.7, 130.0, 129.4, 129.0, 128.7, 128.6, 128.5, 128.4, 127.7, 127.6, 127.1, 126.2, 120.7, 120.1, 119.4, 112.1, 109.4, 101.7, 49.1, 30.9; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2$ (MH^+) 439.2174, found 439.2176.

2-(1-Benzyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (32): White solid, 94% yield; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, 1H, J = 8.3 Hz), 7.62 (d, 2H, J = 9.5 Hz), 7.51-7.11 (m, 17H), 6.95 (dd, 2H, J = 1.5, 8.1 Hz), 6.75-6.72 (m, 2H), 6.51 (s, 1H), 6.25 (s, 1H), 5.20 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 139.6, 139.1, 137.9, 136.8, 136.3, 135.2, 133.5, 133.4, 132.2, 130.9, 130.4, 129.4, 129.0, 128.7, 128.5, 128.2, 127.7, 127.5, 127.2, 126.4, 124.2, 123.8, 120.5, 116.0, 114.1, 113.9, 113.0, 49.1; HRMS (ESI^+) m/z calculated for $C_{37}H_{29}N_2O_2S$ (MH^+) 565.1950, found 565.1945.

2-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)-1*H*-indole (33): White solid, 92% yield; ^{1}H NMR ($CDCl_3$) δ 8.11 (br s, 1H), 7.64 (d, 1H, J = 6.6 Hz), 7.40-7.30 (m, 4H), 7.20-7.14 (m, 2H), 7.00 (d, 2H, J = 7.6 Hz), 6.49 (s, 1H), 6.19 (s, 1H), 5.12 (s, 2H), 2.41 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2, 136.0, 135.7, 130.0, 129.1, 128.7, 127.5, 126.1, 125.9, 121.0, 119.9, 119.9, 112.7, 110.5, 105.1, 98.5, 47.2, 25.7, 12.6, 11.7; HRMS (ESI^+) m/z calculated for $C_{21}H_{21}N_2$ (MH^+) 301.1705, found 301.1706.

2-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (34): Pale yellow solid, 70% yield; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 7.8 Hz), 7.42-7.15 (m, 6H), 7.03 (d, 2H, J = 7.3 Hz), 6.45 (s, 1H), 6.10 (s, 1H), 5.15 (s, 2H), 3.78 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 137.8, 129.1, 128.6, 128.1, 127.7, 127.5, 125.9, 120.8, 120.0, 119.5, 111.6, 109.4, 108.0, 101.0, 47.4, 31.0, 12.6, 11.3; HRMS (ESI^+) m/z calculated for $C_{22}H_{23}N_2$ (MH^+) 315.1861, found 315.1864.

2-(1-Benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (35): Light orange solid, 86% yield; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1H, J = 8.3), 7.50-7.07 (m, 13H), 6.40 (s, 1H), 6.09 (s, 1H), 5.08 (s, 2H), 2.26 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.4, 138.1, 138.0, 133.4, 130.9, 129.1, 128.7, 127.5, 127.1, 127.0, 126.1, 124.1, 124.1, 120.3, 116.5, 112.4, 111.1, 110.1, 47.4, 12.6, 11.1; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2O_2S$ (MH^+) 441.1637, found 441.1641.

3-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1*H*-indole (36a): White solid, 51% (obtained as the

major isomer – 77:23 ratio of **36a:36b**); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, J = 7.6 Hz), 7.45-7.08 (m, 11H), 7.00 (d, 2H, J = 7.1 Hz), 6.69 (d, 1H, J = 2.4 Hz), 6.49 (s, 1H), 5.09 (s, 2H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.4, 136.2, 133.9, 131.4, 129.1, 129.0, 128.9, 128.7, 128.5, 127.3, 127.1, 126.0, 122.3, 121.9, 121.9, 120.7, 119.6, 115.3, 112.6, 111.2, 108.4, 47.9, 12.8; HRMS (EI^+) m/z calculated for $C_{26}H_{22}N_2$ (M^+) 362.17830, found 362.17707.

3-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1*H*-indole (36b): Clear oil, 20% (obtained as the major isomer – 63:37 ratio of **36b:36a**); ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.85 (d, 1H, J = 7.8), 7.43-7.06 (m, 14H), 6.62 (s, 1H), 5.26 (s, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.3, 136.4, 134.4, 129.0, 128.9, 128.9, 128.7, 127.3, 127.3, 127.0, 126.0, 122.3, 121.9, 121.8, 120.7, 119.8, 115.1, 113.0, 111.3, 109.7, 48.3, 11.7; HRMS (EI^+) m/z calculated for $C_{26}H_{22}N_2$ (M^+) 362.17830, found 362.17743.

3-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (37a): Orange solid, 86% (obtained as the major isomer – 74:26 ratio of **37a:37b**); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 8.1 Hz), 7.41-7.18 (m, 9H), 7.09 (t, 2H, J = 6.8 Hz), 7.00 (d, 2H, J = 7.6), 6.59 (s, 1H), 6.45 (s, 1H), 5.08 (s, 2H), 3.65 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.5, 137.0, 134.0, 131.3, 129.0, 128.9, 128.5, 127.3, 127.1, 126.6, 126.0, 121.4, 120.9, 119.0, 115.4, 111.2, 109.2, 108.5, 47.9, 32.8, 12.8; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2$ (MH^+) 377.2018, found 377.2021.

3-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (37b): Orange oil, 39% (obtained as the major isomer – 56:44 ratio of **37b:37a**); ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1H, J = 7.8 Hz), 7.50-7.12 (m, 14H), 6.67 (s, 1H), 5.31 (s, 2H), 3.87 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.4, 137.1, 134.3, 131.4, 129.2, 128.9, 128.7, 127.2, 126.9, 126.5, 126.0, 121.8, 120.8, 119.3, 115.3, 111.1, 109.8, 109.4, 48.3, 33.0, 11.7; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2$ (MH^+) 377.2018, found 377.2021.

3-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (38a): Pale orange solid, 71% (obtained as the major isomer – 88:12 ratio of **38a:38b**); ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1H, J = 8.3 Hz), 7.67 (d, 2H, J = 7.8 Hz), 7.50-7.19 (m, 13H), 7.08 (s, 1H), 6.96 (d, 2H, J = 7.1 Hz), 6.39 (s, 1H), 5.07 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.3, 135.4, 133.7, 133.1, 131.7, 131.2, 129.7, 129.3, 129.1, 129.0, 128.7, 127.9, 127.3, 127.0, 126.0, 124.7, 123.6, 122.8, 121.3, 119.4, 113.8, 112.8, 108.2, 48.0, 12.8; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2O_2S$ (MH^+) 503.1793, found 503.1789.

3-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (38b): Orange solid, 65% (obtained as the major isomer – 51:49 ratio of **38b:38a**); ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 8.3

Hz), 7.94 (d, 2H, J = 7.6 Hz), 7.77 (d, 2H, J = 7.6 Hz), 7.66 (d, 2H, J = 7.6 Hz), 7.54-7.18 (m, 10H), 7.04 (d, 2H, J = 7.1 Hz), 6.55 (s, 1H), 5.24 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.3, 135.4, 133.6, 133.0, 131.4, 131.3, 129.7, 129.3, 129.1, 129.0, 128.7, 127.9, 127.3, 127.0, 125.9, 124.6, 123.4, 122.5, 121.3, 119.4, 113.8, 112.7, 108.2, 48.0, 11.7; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2O_2S$ (MH^+) 503.1793, found 503.1795.

2-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1*H*-indole (39a): Off-white solid, 89% (obtained as the major isomer – 87:13 ratio of **39a:39b**); ^{1}H NMR ($CDCl_3$) δ 7.68 (br s, 1H), 7.53-7.25 (m, 8H), 7.15-7.03 (m, 3H), 6.94 (d, 2H, J = 7.1 Hz), 6.43 (s, 1H), 6.40 (d, 1H, J = 1.7 Hz), 4.98 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.9, 135.1, 133.1, 131.6, 130.2, 130.1, 129.2, 129.1, 129.0, 128.9, 128.8, 127.4, 125.9, 125.9, 120.9, 119.8, 119.7, 114.0, 110.4, 106.4, 98.3, 47.7, 12.7; HRMS (ESI^+) m/z calculated for $C_{26}H_{23}N_2$ (MH^+) 363.1861, found 363.1862.

2-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1*H*-indole (39b): Off-white solid, 62% (obtained as the major isomer – 74:26 ratio of **39b:39a**); ^{1}H NMR ($CDCl_3$) δ 8.16 (br s, 1H), 7.64 (d, 2H, J = 7.1 Hz), 7.38-7.02 (m, 12H), 6.54-6.52 (m, 2H), 5.23 (s, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7, 136.1, 135.1, 133.3, 131.6, 129.9, 129.2, 129.1, 129.0, 128.9, 128.8, 127.6, 127.5, 125.9, 125.9, 121.3, 120.1, 119.8, 114.3, 110.6, 107.1, 99.0, 48.2, 11.9; HRMS (ESI^+) m/z calculated for $C_{26}H_{23}N_2$ (MH^+) 363.1861, found 363.1859.

2-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (40a): Yellow solid, 76% (obtained as the major isomer – 90:10 ratio of **40a:40b**); ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H, J = 7.8 Hz), 7.39-6.99 (m, 13H), 6.34 (s, 1H), 6.23 (s, 1H), 5.15 (s, 2H), 3.40 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.0, 137.6, 132.9, 130.5, 129.8, 129.1, 129.1, 128.8, 128.6, 128.6, 127.5, 127.4, 125.9, 120.6, 120.0, 119.3, 113.5, 110.1, 109.4, 101.5, 48.1, 30.8, 12.8; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2$ (MH^+) 377.2018, found 377.2019.

2-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-indole (40b): Yellow oil, 45% (obtained as the minor isomer – 30:70 ratio of **40b:40a**); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 7.6 Hz), 7.40-7.00 (m, 13H), 6.49 (s, 1H), 6.44 (s, 1H), 5.26 (s, 2H), 3.80 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.6, 132.8, 130.5, 129.8, 129.1, 129.0, 128.8, 128.7, 128.6, 127.5, 127.4, 125.9, 120.9, 120.1, 119.6, 113.4, 110.1, 109.5, 101.3, 48.4, 31.0, 11.5; HRMS (ESI^+) m/z calculated for $C_{27}H_{25}N_2$ (MH^+) 377.2018, found 377.2018.

2-(1-Benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (41a): Tan solid, 95% (obtained as the major isomer – 79:21 ratio of **41a:41b**); ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H, J = 8.5 Hz), 7.63-7.12 (m, 13H), 7.02-6.97 (m, 5H), 6.28 (s, 1H), 6.23 (s, 1H), 5.09 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.6, 138.9, 137.8, 137.5, 134.2, 133.5, 132.5, 130.8, 129.1, 129.0, 129.0, 128.9, 128.8, 128.8, 128.3, 127.4, 127.2, 127.1, 124.1, 123.8, 120.5, 116.0, 113.0, 111.7, 48.1, 12.8; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2O_2S$ (MH^+) 503.1793, found 503.1801.

2-(1-Benzyl-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)-1-(phenylsulfonyl)-1*H*-indole (41b): Tan solid, 78% (obtained as the major isomer – 91:9 ratio of **41b:41a**); ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 1H, J = 8.1 Hz), 7.53-7.10 (m, 18H), 6.49 (s, 1H), 6.39 (s, 1H), 5.22 (s, 2H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.8, 138.1, 137.4, 133.5, 131.5, 130.8, 129.1, 129.1, 128.9, 128.9, 128.7, 128.7, 128.3, 127.5, 127.3, 127.1, 126.1, 124.3, 124.1, 120.4, 116.5, 112.6, 112.2, 48.3, 11.5; HRMS (ESI^+) m/z calculated for $C_{32}H_{27}N_2O_2S$ (MH^+) 503.1793, found 503.1797.

ACKNOWLEDGEMENTS

This work was supported by the Donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, and by Wyeth.

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