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Expedient synthesis of tetrasubstituted pyrroles *via* copper-catalyzed cascade inter-/intramolecular cyclization of 1,3-enynes carry a nitro group with amines

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Various tetrasubstituted pyrroles/pyrazoles have been prepared from nitro-substituted 1,3-enynes with aromatic amines/hydrazines *via* a copper-catalyzed cascade aza-Michael addition, cyclization and aromatization at room temperature. This protocol is also effective for the synthesis of tetrasubstituted pyrazoles in high yields.

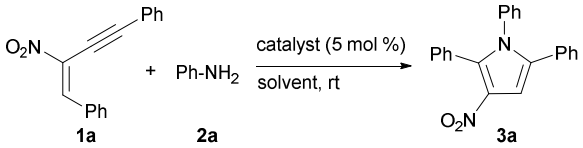
Introduction

Pyrroles are among the most important class of heterocycles that frequently found in natural products[1] and pharmaceuticals.[2] This heterocyclic core also serve as key intermediates in the synthesis of biologically important molecules and functional materials.[3] The anticancer drug tallimustine and the blockbuster lipid-lowering drug atorvastatin calcium (Lipitor) are the prime examples.[4] As a result, many synthetic methods have been developed for the synthesis of pyrrole rings or its related structural motifs.[5,6] Among these, the transition-metal-catalyzed processes have attracted significant interest due to their versatility.[6] Despite these developments, the strategies for the synthesis of polysubstituted pyrroles with diverse substituents from the readily available substrate precursors are somewhat limited due to lack of selectivity and harsh reaction conditions.[7] In continuation of our studies on heterocycle syntheses,[8] we report here the synthesis of tetrasubstituted pyrroles from 1,3-enynes with amines *via* an aerobic copper-catalyzed cascade aza Michael addition,[9] cyclization and oxidation at room temperature. This protocol is efficient, atom economical and tolerates an array of functionality and substantial steric hindrance, and is also effective for the synthesis of medicinally significant analogue tetrasubstituted pyrazoles in high yields.

Results and discussion

First, the reaction conditions were optimized employing (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne **1a** and aniline **2a** as the model substrates in the presence of copper catalysts in different solvents under air (Table 1). To our delight, the reaction

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

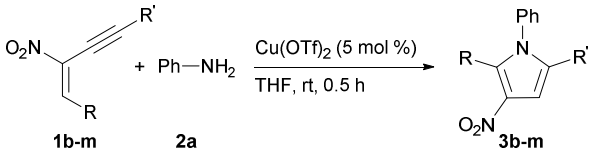
Entry	Catalyst	Solvent	Conversion[b]
1	CuCl	THF	84
2	CuBr	THF	89
3	CuI	THF	92
4	$Cu(OAc)_2$	THF	95
5	**$Cu(OTf)_2$**	**THF**	**99[c] (87[d])**
6	$CuSO_4$	THF	25
7	$Cu(OTf)_2$	CH_3CN	74
8	$Cu(OTf)_2$	toluene	88
9	$Cu(OTf)_2$	CH_2Cl_2	81
10	-	THF	n.d.

[a] Reaction conditions: 0.5 mmol of **1a**, 0.6 mmol of **2a**, catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 2 h. [b] Determined by ^1H NMR spectroscopic analysis. [c] The reaction completed at 0.5 h. [d] Isolated yield. n.d.= not detected.

efficiently occurred to furnish the target 3-nitro-1,2,5-triphenyl-1*H*-pyrrole **3a** in 0.5 h up to 99% conversion when the substrates were stirred with 5 mol % $Cu(OTf)_2$ in THF at room temperature under air. In a set of copper sources screened, $Cu(OTf)_2$ exhibited the superior results, while CuCl, CuBr, CuI and $Cu(OAc)_2$ required slightly longer reaction (2 h) to afford

similar conversions (entries 1-5). In contrast, the reaction using $CuSO_4$ was less effective yielding **3a** in 25% conversion (entry 6). THF was found to be solvent of choice giving the best results, whereas CH_3CN, CH_2Cl_2 and toluene led to the formation of **3a** in 74-88% conversions (entries 7-9). Control experiment confirmed that the target heterocycle **3a** was not formed in the absence of the copper catalyst.

Table 2 Cu(II)-catalyzed cascade cyclization of several 1,3-enynes with aniline[a]



Entry	1	R	R'	3	Yield (%)[b]
1	**1b**	Ph	4-ClC_6H_4	**3b**	69
2	**1c**	Ph	4-$MeOC_6H_4$	**3c**	80
3	**1d**	Ph	3,4-$Me_2C_6H_3$	**3d**	75
4	**1e**	Ph	3,5-$Me_2C_6H_3$	**3e**	72
5	**1f**	Ph	1-naphthyl	**3f**	63
6	**1g**	2-MeC_6H_4	Ph	**3g**	74
7	**1h**	2-$MeOC_6H_4$	Ph	**3h**	80
8	**1i**	3-MeC_6H_4	Ph	**3i**	79
9	**1j**	4-FC_6H_4	Ph	**3j**	81
10	**1k**	4-$MeOC_6H_4$	Ph	**3k**	83
11	**1l**	4-MeC_6H_4	Ph	**3l**	76
12	**1m**	1-naphthyl	Ph	**3m**	82

[a] Reaction conditions: 0.5 mmol of **1b-m**, 0.6 mmol of **2a**, catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 0.5 h. [b] Isolated yield.

Having the optimal conditions, the scope of the protocol was explored for the reaction of various 1,3-enyne derivatives **1b-m** with aniline **2a** as a standard substrate (Table 2). The reactions readily occurred in high yields. For example, the enynes **1b-c**, **1h** and **1j-k** bearing electron donating and electron withdrawing substituents, chloro, flouro and methoxy groups, underwent reaction in 69-83% yields. In addition, the mono and dimethyl substituted enynes **1d-e**, **1g**, **1i** and **1l** proceeded reaction in 72-79% yields. Furthermore, the reactions of the enynes **1f** and **1m** with naphthyl substituent produced the pyrrole derivatives **3f** and **3m** in 63% and 82% yields, respectively.

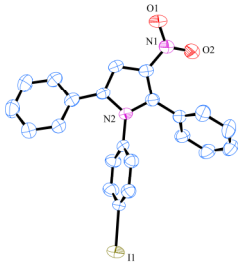
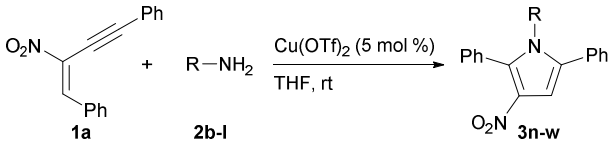


Fig. 1 ORTEP diagram of 1-(4-iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole **3o**. Thermal ellipsoids are drawn at a 50% probability level. Hydrogen atoms have omitted for clarity (CCDC 1025795).

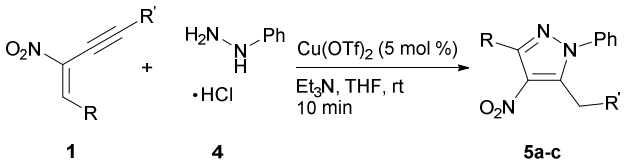
Table 3 Cu(II)-catalyzed cascade cyclization of (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne with different amines[a]



Entry	2	R	Time (h)	3	Yield (%)[b]
1	**2b**	4-ClC_6H_4	1.5	**3n**	78
2	**2c**	4-IC_6H_4	1.0	**3o**	82
3	**2d**	4-$MeOC_6H_4$	0.5	**3p**	71
4	**2e**	4-MeC_6H_4	0.5	**3q**	92
5	**2f**	4-$NO_2C_6H_4$	18	**3r**	76
6	**2g**	2,4-$Me_2C_6H_3$	0.5	**3s**	88
7	**2h**	3,4-$Me_2C_6H_3$	0.5	**3t**	90
8	**2i**	3-MeC_6H_4	0.5	**3u**	77
9	**2j**	4-$C_6H_4N_2Ph$	0.5	**3v**	76
10	**2k**	2-fluorenyl	0.5	**3w**	53
11	**2l**	*i*Pr	24	**3x**	n.d.

[a] Reaction conditions: 0.5 mmol of **1a**, 0.6 mmol of **2b-l**, catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for appropriate time. [b] Isolated yield. n.d. = not detected.

Table 4 Cu(II)-catalyzed cyclization 1,3-enynes with phenyl hydrazine[a]



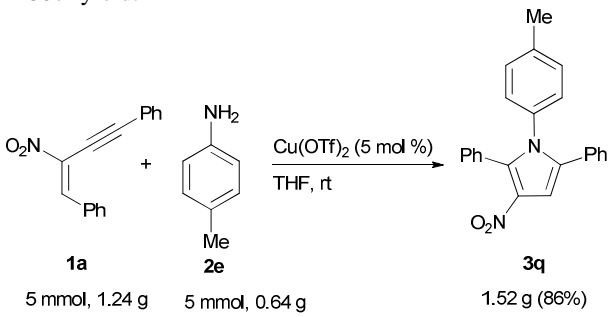
Entry	1	R	R'	5	Yield (%)[b]
1	**1a**	Ph	Ph	**5a**	93
2	**1i**	3-MeC_6H_4	Ph	**5b**	86
3	**1m**	1-naphthyl	Ph	**5c**	75

[a] Reaction conditions: 0.5 mmol of **1**, 0.6 mmol of **4**, Et_3N (2.0 equiv), catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 10 min. [b] Isolated yield.

Next, the reaction of various substituted amines **2b-l** was studied using (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne **1a** as a standard substrate (Table 3). As above, the reactions readily occurred in high yields. For examples, aryl amines **2b-i** having electron withdrawing and electron donating groups, chloro, iodo, methoxy, methyl and nitro groups, underwent reaction to give the corresponding substituted pyrroles **3n-u** in 71-92% yields. Aniline **2f** with strong electron withdrawing nitro group was less reactive, which may be due to its weak nucleophilicity. Crystallization of 1-(4-Iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole **3o** in MeOH gave a single crystal whose structure was confirmed by X-ray analysis (Fig. 1). Furthermore, amine **2j** with diazophenyl group proceeded reaction in 76% yield, whereas the reaction of 2-fluorenyl amine **2k** furnished the target pyrrole derivative **3w** in 53% yield. In contrast, the reaction with aliphatic amine **2l** showed no product formation, which may due to the complex formation with $Cu(OTf)_2$.

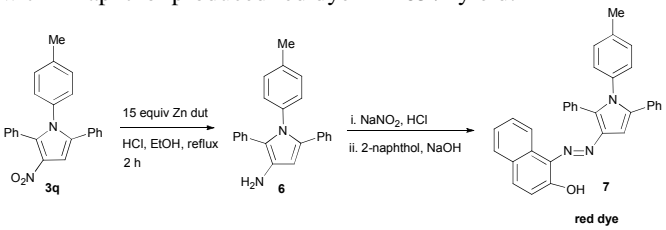
Finally, the compatibility of the protocol was examined for the synthesis of analogue substituted pyrazoles[10] using phenylhydrazine **4** (Table 4). As anticipated, the reaction readily occurred in high yields. For examples, the enynes **1a**, **1i** and **1m** underwent reaction to produce the corresponding pyrazole derivatives **5a-c** in 75-93% yields. This reaction exhibited greater reactivity compared to that of the pyrrole synthesis. These results suggest that this protocol can be utilized for the synthesis of tetrasubstituted pyrroles and pyrazoles with broad substrate scope and substantial steric hindrance at mild reaction conditions.

The scale of the procedure was examined using 1,3-enyne **1a** and 4-methylaniline **2e** as representative examples (Scheme 1). The reaction readily occurred to afford the target product **3q** in 86% yield.



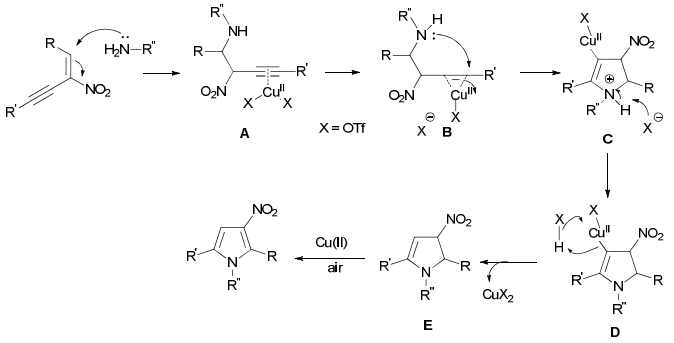
Scheme 1 Gram scale synthesis.

The synthetic utility of the pyrrole derivative was studied for the preparation of azo dye (Scheme 2). Treatment of **3q** with 15 equiv of Zn dust in the presence of HCl in EtOH gave amine **6** in 81% yield. Diazotization of **6** followed by coupling with 2-naphthol produced red dye **7** in 63% yield.



Scheme 2 Preparation of azo dye.

The proposed catalytic cycle is shown in Scheme 3. Aza-Michael addition of aryl amines with the electron deficient 1,3-enynes in the presence of the Lewis acid copper(II) may lead to the formation of the intermediate **B** via **A**. Intramolecular 5-endo-dig cyclization[6w] of **B** can give intermediate **C** that can convert into the intermediate **D**. The latter can transform into dihydropyrrole derivative **E** and CuX_2. The oxidation of the intermediate **E** can give the target products, and the copper(I) species, which can be reoxidized by air into copper(II) species to complete the catalytic cycle.



Scheme 3 Plausible mechanism for the formation of pyrroles.

Conclusion

Copper-catalyzed cascade reaction of 1,3-enynes with amines has been developed for the synthesis of tetrasubstituted pyrroles/pyrazoles using air as oxidant. Broad substrate scope, atom economy, mild reaction conditions, eco-friendliness and shorter reaction time are the significant practical advantages.

Experimental

General

Amines, aldehydes, $Pd(PPh_3)_2Cl_2$ (98%), PPh_3 (99%), CuCl (99%), CuBr (98%), CuI (98%), $Cu(OTf)_2$ (98%) and $Cu(OAc)_2$ (98%), $CuSO_4$ (99.99%) were purchased from Aldrich and used as received. The progress of the reaction was monitored by analytical TLC on Merck silica gel G/GF 254 plates. The column chromatography was performed with Rankem silica gel 60-120 mesh. NMR (^1H and ^{13}C) spectra were recorded on 400 and 600 MHz instruments using $CDCl_3$ as a solvent and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm, and spin–spin coupling constants (*J*) were given in Hz. The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. High-resolution mass spectra were recorded on a QTof ESI-MS instrument. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods using SHELLX-97 (Göttingen, Germany) and refined with full-matrix least squares on F2 using SHELXL-97. 1,3-Enynes **1a-m** were prepared according to the reported procedure.[11]

General procedure for synthesis of substituted pyrroles

To a stirred solution of amine (0.6 mmol) and $Cu(OTf)_2$ (5 mol %) in THF (2 mL) was added a solution of 1,3-enynes (0.5 mmol) in THF (1.0 mL) at room temperature under air, and the stirring was continued until completion of the reaction. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The resultant mixture was then concentrated using rotary evaporator to give a residue, which

was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent.

General procedure for synthesis of substituted pyrazoles

To a stirred solution of phenyl hydrazine hydrochloride (0.6 mmol) and Et_3N (1.0 mmol) in THF (1mL) was added $Cu(OTf)_2$ (5 mol %) at room temperature under air. After 5 min, a solution of 1,3-enynes (0.5 mmol) in THF (1.0 mL) was added, and the stirring was continued until completion of the reaction. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as solvent. Evaporation of the solvent gave a residue that was treated with water (5 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the combined CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated on a rotary evaporation to give a residue, which was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent.

3-Nitro-1,2,5-triphenyl-1*H*-pyrrole 3a. Yellow solid; yield 87%; mp 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.17 (m, 11H), 7.10-7.08 (m, 3H), 6.94 (dd, *J* = 7.6, 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.2, 134.9, 134.4, 131.2, 131.0, 129.5, 129.4, 129.0, 128.9, 128.8, 128.5, 128.4, 128.0, 127.9, 106.0; FT-IR (KBr) 3114, 3072, 3034, 2923, 1551, 1527, 1495, 1468, 1449, 1397, 1375, 1321, 1305, 1183, 1027, 833, 782, 762, 755, 697 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{16}N_2O_2$ 341.1290, found 341.1292.

5-(4-Chlorophenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole 3b. Yellow solid; yield 69%; mp 206-207 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.16 (m, 10H), 7.08 (s, 1H), 7.01-6.98 (m, 2H), 6.92-6.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.5, 134.9, 134.0, 133.1, 131.1, 130.1, 129.5, 129.3, 129.2, 129.0, 128.8, 128.7, 128.0, 106.2; FT-IR (KBr) 3134, 3056, 1554, 1526, 1492, 1468, 1447, 1418, 1388, 1317, 1308, 1189, 1092, 1011, 919, 835, 804, 770, 756, 742, 698 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{15}ClN_2O_2$ 375.0900, found 375.1010.

5-(4-Methoxyphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole 3c: Yellow solid; yield 80%; mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.17 (m, 8H), 7.01(d, *J* = 8.0 Hz, 3H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 136.6, 134.4, 133.9, 130.8, 129.9, 129.1, 128.6, 128.5, 128.4, 128.0, 127.5, 123.1, 113.5, 104.9, 54.9; FT-IR (KBr) 3125, 3050, 3006, 2973, 2928, 2842, 1612, 1560, 1498, 1469, 1453, 1445, 1397, 1321, 1306, 1287, 1247, 1183, 1028, 833, 807, 795, 778, 728, 707, 702 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1396.

5-(3,4-Dimethylphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole 3d. Yellow solid; yield 75%; mp 174-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.16 (m, 8H), 7.04 (s, 1H), 6.93 (s, 4H), 6.71 (d, *J* = 7.6 Hz, 1H), 2.18 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.7, 136.5, 135.0, 134.9, 134.7, 131.2, 130.2, 129.6, 128.9, 128.8, 128.5, 128.4, 127.9, 126.3, 105.5, 19.8, 19.6; FT-IR (KBr) 3142, 3059, 3009, 2961, 2911, 2853, 1596, 1526, 1494, 1469, 1445, 1417, 1388, 1320, 1306, 1201, 1168, 918, 821, 802, 774, 763, 754, 701, 691 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1601.

5-(3,5-Dimethylphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole 3e. Yellow solid; yield 72%; mp 216-217 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.16 (m, 8H), 7.06 (s, 1H), 6.93-6.92 (m, 2H), 6.85 (s, 1H), 6.68 (s, 2H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.1, 135.0, 134.9, 134.7, 131.2, 130.8, 129.6, 129.0, 128.9, 128.4, 127.9, 126.8, 105.7, 21.3; FT-IR (KBr) 3070, 2909, 2848, 1598, 1560, 1536, 1493, 1483, 1470, 1395, 1323, 1310, 1230, 1080, 1007, 857, 810, 778, 770, 754, 710, 696 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1595.

5-(Naphthalen-1-yl)-3-nitro-1,2-diphenyl-1*H*-pyrrole 3f. Yellow solid; yield 63%; mp 242-243 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98-7.97 (m, 1H), 7.81 (dd, *J* = 7.2, 3.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.50-7.46 (m, 2H), 7.31-7.26 (m, 6H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.15 (s, 1H), 7.00-6.98 (m, 1H), 6.94 (t, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.7, 133.5, 132.9, 132.2, 131.2, 129.9, 129.5, 129.2, 128.9, 128.6, 128.4, 128.3, 128.1, 128.0, 126.8, 126.2 125.7, 124.9, 108.1; FT-IR (KBr) 3056, 1826, 1497, 1491, 1478, 1469, 1445, 1395, 1318, 1305, 848, 802, 768, 756, 714, 701, 696 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{26}H_{18}N_2O_2$ 391.1447, found 391.1446.

3-Nitro-1,5-diphenyl-2-(*o*-tolyl)-1*H*-pyrrole 3g. Yellow solid; yield 74%; mp 166-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.19 (m, 5H), 7.16-7.10 (m, 6H), 7.06 (d, *J* = 4.0 Hz, 2H), 6.92 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.0, 135.4, 135.3, 134.4, 131.1, 129.9, 129.5, 129.4, 128.9, 128.8, 128.6, 128.5, 128.3, 127.9, 125.4, 105.7, 20.1; FT-IR (KBr) 3131, 3070, 2917, 2845, 1598, 1559, 1490, 1473, 1456, 1445, 1401, 1317, 1306, 1284, 1254, 1188, 1132, 1080, 1027, 955, 919, 839, 802, 782, 766, 758, 733, 701, 696 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1445.

2-(2-Methoxyphenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole 3h. Yellow solid; yield 80%; mp 171-172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.27 (m, 1H), 7.21-7.08 (m, 10H), 6.95 (d, *J* = 7.2, 2H), 6.86 (t, *J* = 7.2, 1H), 6.79 (d, *J* = 8.4, 1H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 137.3, 134.3, 132.5, 132.4, 131.2, 130.9, 128.9, 128.8, 128.6, 128.4, 128.3, 127.9, 127.7, 120.3, 119.0, 110.9, 105.9, 55.5; FT-IR (KBr) 3125, 3050, 2961, 2925, 2837, 1611, 1596, 1560, 1491, 1478, 1460, 1446, 1404, 1321, 1309, 1275, 1247, 1047, 1024, 836, 780, 770, 753, 700 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1394.

3-Nitro-1,5-diphenyl-2-(*m*-tolyl)-1*H*-pyrrole 3i. Yellow solid; yield 79%; mp 190-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.15 (m, 6H), 7.13-7.00 (m, 7H), 6.94 (d, *J* = 6.8 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.0, 135.5, 134.8, 134.3, 131.8, 131.1, 129.7, 129.3, 129.0, 128.98, 128.90, 128.5, 128.4, 128.2, 127.9, 127.8, 106.0, 21.4; FT-IR (KBr) 3120, 3047, 3014, 2914, 2850, 1601, 1551, 1526, 1490, 1477, 1446, 1393, 1322, 1307, 1171, 1018, 930, 857, 822, 818, 798, 768, 697 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1443.

2-(4-Fluorophenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole 3j. Yellow solid; yield 81%; mp 186-187°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.18 (m, 8H), 7.08-7.07 (m, 3H), 6.96-6.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (d, J_{C-F} = 248.6 Hz), 136.8, 135.1, 134.6, 134.0, 133.2 (d, J_{C-F} = 8.4 Hz), 130.9, 129.2, 129.0, 128.8, 128.7, 128.4, 128.0, 125.4, 115.3 (d, J_{C-F} = 22.1 Hz), 106.0; FT-IR (KBr) 3139, 3061, 3022, 1599, 1508, 1497, 1448, 1418, 1398, 1325, 1226, 1187, 1163, 1026, 846, 824, 811, 784, 763, 752, 734, 703, 695 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{15}FN_2O_2$ 359.1196, found 359.1189.

2-(4-Methoxyphenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole 3k. Yellow solid; yield 83%; mp 186-187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.08 (m, 11H), 6.93 (d, *J* = 6.8 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.0, 135.2, 134.9, 134.2, 132.6, 131.1, 129.1, 129.0, 128.9, 128.5, 128.4, 127.9, 121.4, 113.5, 106.1, 55.3; FT-IR (KBr) 3134, 3061, 2939, 2842, 1608, 1574, 1506, 1477, 1463, 1445, 1415, 1399, 1319, 1304, 1289, 1253, 1176, 1026, 843, 827, 781, 769, 760, 737, 698 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1393.

3-Nitro-1,5-diphenyl-2-(*p*-tolyl)-1*H*-pyrrole 3l. Yellow solid; yield 76%; mp 176-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.16 (m, 6H), 7.10-7.05 (m, 7H), 6.93 (d, *J* = 7.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.0, 135.4, 134.9, 134.3, 131.1, 131.0, 129.0, 128.9, 128.7, 128.5, 128.4, 127.9, 126.3, 106.1, 21.5; FT-IR (KBr) 3117, 3081, 3050, 3022, 2928, 1560, 1506, 1473, 1446, 1415, 1393, 1377, 1321, 1315, 1306, 1177, 1016, 845, 823, 785, 768, 758, 733, 702, 696 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1445.

2-(Naphthalen-1-yl)-3-nitro-1,5-diphenyl-1*H*-pyrrole 3m. Yellow solid; yield 82%; mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 7.68-7.67 (m, 1H), 7.48-7.45 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.24-6.99 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.2, 134.8, 133.7, 133.2, 133.0, 131.0, 129.7, 129.5, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.6, 127.0, 126.2, 125.1, 124.8, 105.7; FT-IR (KBr) 3150, 3045, 1596, 1559, 1534, 1508, 1497, 1481, 1454, 1447, 1407, 1319, 1305, 1264, 1217, 1068, 917, 807, 793, 781, 772, 756, 726, 697 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{26}H_{18}N_2O_2$ 391.1447, found 391.1449.

1-(4-Chlorophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3n. Yellow solid; yield 78%; mp 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.19 (m, 8H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.06 (s, 3H), 6.86 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 135.0, 134.5, 134.4, 131.1, 130.7, 130.0, 129.3, 129.1, 129.0, 128.6, 128.1, 106.2; FT-IR (KBr) 3134, 3097, 3056, 3039, 1560, 1497, 1470, 1449, 1444, 1400, 1320, 1310, 1182, 1094, 1010, 952, 846, 818, 758, 727, 700 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{15}ClN_2O_2$ 375.0900, found 375.0862.

1-(4-Iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3o. Yellow solid; yield 82%; mp 189-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.29-7.18 (m, 8H), 7.06 (s, 3H), 6.65 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.6, 134.9, 134.3, 131.2, 130.7, 130.5, 129.2, 129.1, 129.0, 128.6, 128.2, 106.3, 94.0; FT-IR (KBr) 3145, 3081, 3042, 2964, 1601, 1552, 1491, 1472, 1448, 1402, 1318, 1306, 1279, 1259, 1008, 821, 774, 759, 733, 723, 694 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{15}IN_2O_2$ 467.0256, found 467.0247.

1-(4-Methoxyphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3p. Yellow solid; yield 71%; mp 130-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 8H), 7.11-7.09 (m, 2H), 7.07 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 135.4, 134.8, 134.5, 131.23, 131.20, 129.8, 129.7, 129.6, 129.0, 128.8, 128.4, 128.0, 127.8, 114.1, 105.8, 55.5; FT-IR (KBr) 3150, 3059, 2978, 2925, 2828, 1612, 1561, 1515, 1494, 1447, 1405, 1387, 1324, 1297, 1252, 1178, 1168, 1022, 846, 831, 813, 799, 763, 753, 734, 697 cm^{-1} ; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1378.

3-Nitro-2,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole 3q. Yellow solid; yield 92%; mp 181-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (m, 8H), 7.09-7.06 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.3, 134.8, 134.4, 134.2, 131.2, 131.1, 129.6, 129.5, 128.9, 128.8, 128.5, 128.4, 127.9, 127.8, 105.9, 21.2; FT-IR (KBr) 3120, 3067, 3039, 2920, 2956, 2853, 1554, 1513, 1500, 1448, 1403, 1324, 1186, 840, 819, 760, 731, 696, 546 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1443.

3-Nitro-1-(4-nitrophenyl)-2,5-diphenyl-1*H*-pyrrole 3r. Yellow solid; yield 76%; mp 165-166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.33-7.19 (m, 9H), 7.08-7.04 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.0, 142.4, 135.6, 134.8, 134.4, 131.1, 130.3, 129.7, 129.5, 129.1, 128.8, 128.7, 128.5, 128.4, 124.3, 106.8; FT-IR (KBr) 3145, 3120, 3064, 3039, 2859, 1613, 1597,1523, 1498, 1474, 1448, 1400, 1346, 1320, 1182, 1107, 909, 864, 854, 831, 775, 753, 733, 716, 701 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{15}N_3O_4$ 386.1141, found 386.1150.

1-(2,4-Dimethylphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3s. Yellow solid; yield 88%; mp 185-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 8H), 7.09 (s, 3H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 2.20 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7, 135.3, 134.7, 134.6, 133.4, 131.6, 131.2, 130.8, 129.6, 129.4, 128.9, 128.4, 127.9, 127.2, 105.6, 21.2, 17.7; FT-IR (KBr) 3134, 3056, 3031, 2911, 1604, 1565, 1535, 1494, 1471, 1448, 1405, 1319, 1261, 1236, 1187, 1027, 837, 820, 763, 738, 698 cm^{-1}; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1596.

1-(3,4-Dimethylphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3t. Yellow solid; yield 90%; mp 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 8H), 7.09-7.05 (m, 3H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.66-6.62 (m, 2H), 2.13 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 137.0, 135.3, 134.7, 134.4, 131.2, 131.1, 129.9, 129.7, 129.6, 128.9, 128.7, 128.3, 127.9, 127.7, 126.0, 105.8, 19.7, 19.5; FT-IR (KBr) 3120, 3053, 3031, 2973, 2914, 2853, 1602, 1579, 1553, 1530, 1496, 1472, 1404, 1375, 1322, 1309, 1190, 1029, 918, 889, 875, 839, 821,

774, 759, 731, 707, 692 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1572.

3-Nitro-2,5-diphenyl-1-(*m*-tolyl)-1*H*-pyrrole 3u. Yellow solid; yield 77%; mp 164-165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 8H), 7.08-6.98 (m, 5H), 6.70 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.8, 135.2, 134.8, 134.4, 131.2, 131.1, 129.5, 129.4, 129.2, 129.0, 128.9, 128.7, 128.4, 127.93, 127.90, 125.9, 105.9, 21.2; FT-IR (KBr) 3147, 3056, 3034, 2917, 1604, 1559, 1469, 1448, 1402, 1281, 1267, 1180, 1163, 1074, 1027, 921, 861, 822, 792, 694 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1440.

(*E*)-3-Nitro-2,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1*H*-pyrrole 3v. Yellow solid; yield 76%; mp 154-155 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 6.49 (s, 3H), 7.28-7.23 (m, 8H), 7.14-7.12 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.6, 138.8, 135.1, 134.4, 131.8, 131.2, 130.8, 129.6, 129.3, 129.2, 129.18, 129.12, 128.6, 128.1, 123.4, 123.1, 106.3; FT-IR (KBr) 3120, 3072, 3025, 2959, 1500, 1485, 1473, 1443, 1404, 1324, 1261, 1180, 1153, 1096, 1068, 1027, 1016, 923, 857, 829, 810, 778, 768, 764, 757, 741, 718, 699, 686 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{28}H_{20}N_4O_2$ 445.1665, found 445.1652.

1-(9*H*-Fluoren-2-yl)-3-nitro-2,5-diphenyl-1*H*-pyrrole 3w. Yellow liquid; yield 53%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.26 -7.23 (m, 5H), 7.20-7.18 (m, 3H), 7.14-7.08 (m, 3H), 7.08 (s, 1H), 6.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.7, 141.9, 140.5, 135.45, 135.41, 134.9, 134.5, 131.2, 131.1, 129.6, 129.0, 128.9, 128.4, 128.0, 127.9, 127.7, 127.6, 127.2, 125.5, 125.3, 120.4, 120.0, 106.0, 36.9; FT-IR (neat) 3136, 3057, 2900, 2792, 1606, 1558, 1496, 1470, 1458, 1448, 1403, 1320, 1264, 1190, 1071, 1029, 1002, 952, 917, 875, 837, 757, 737, 721, 697 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{29}H_{20}N_2O_2$ 429.1603, found 429.1605.

5-Benzyl-4-nitro-1,3-diphenyl-1*H*-pyrazole 5a. Yellow liquid; yield 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.2, 3.2 Hz, 2H), 7.49-7.46 (m, 5H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.28-7.26 (m, 4H), 7.05 (d, *J* = 6.8 Hz, 2H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 143.1, 138.1, 136.0, 130.6, 130.0, 129.6, 129.5, 129.0, 128.6, 128.3, 128.2, 127.2, 126.3, 125.5, 31.5; FT-IR (neat) 3062, 3030, 2925, 2850, 1596, 1552, 1496, 1453, 1438, 1422, 1379, 1357, 1200, 1074, 1027, 1003, 989, 918, 833, 734, 694 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_3O_2$ 356.1399, found 356.1402.

5-Benzyl-4-nitro-1-phenyl-3-(*m*-tolyl)-1*H*-pyrazole 5b. Yellow liquid; yield 86%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.50 (m, 5H), 7.40-7.25 (m, 7H), 7.07 (d, *J* = 7.2 Hz, 2H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 143.1, 138.1, 138.0, 136.0, 130.4, 130.2, 129.9, 129.9, 129.6, 128.9, 128.2, 128.2, 127.2, 126.5, 126.3, 125.4, 31.5, 21.5; FT-IR (neat) 3062, 3030, 2928, 2856, 1596, 1551, 1495, 1457, 1423, 1357, 1279, 1235, 1173, 1073, 1030, 1015, 907, 829, 791, 766, 734, 694 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_2$ 370.1556, found 370.1567.

5-Benzyl-3-(naphthalen-1-yl)-4-nitro-1-phenyl-1*H*-pyrazole 5c. Yellow liquid; yield 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 6.8 Hz, 1H), 7.55 (t, 1H), 7.51-7.42 (m, 7H), 7.30-7.23 (m, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 142.6, 138.1, 136.1, 133.6, 132.1, 130.0, 129.9, 129.6, 129.0, 128.7, 128.3, 128.2, 127.2, 126.8, 126.2, 126.1, 125.2, 125.0, 124.6, 31.5; FT-IR (neat) 3059, 3025, 2934, 1596, 1552, 1494, 1454, 1443, 1387, 1357, 1261, 1225, 1172, 1125, 1070, 1023, 964, 917, 864, 843, 804, 778, 733, 695 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}N_3O_2$ 406.1556, found 406.1559.

2,5-Diphenyl-1-*p*-tolyl-1*H*-pyrrol-3-amine 6. To a stirred solution of **3q** (2 mmol) in ethanol (35 mL) was added zinc dust (30 mmol) and 6 M HCl (10 mL).[12a] After refluxing the mixture for 2 h, cooled to room temperature and diluted with CH_2Cl_2 (10 mL). Excess zinc was filtered and the solvent was evaporated on a rotary evaporator. The residue was neutralized with 15% NaOH (pH 10) and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layer was washed with brine (5 mL x 1), water (5 mL x 1) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was crystallized in hot ethanol. Yellow solid; yield 81%; mp 165-166 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 2H), 7.17-7.11 (m, 4H), 7.07-7.05 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.14 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 136.5, 133.4, 133.3, 132.3, 130.2, 129.8, 129.3, 128.8, 127.7, 128.3, 128.0, 126.2, 125.9, 120.5, 102.6, 21.2; FT-IR (KBr) 3450, 2959, 2922, 2854, 1654, 1600, 1509, 1457, 1418, 1387, 1310, 1261, 1096, 1025, 912, 805, 760, 696 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}N_2$ 325.1705, found 325.1708.

(*E*)-1-((2,5-Diphenyl-1-*p*-tolyl-1*H*-pyrrol-3-yl)diazenyl)naphthalen-2-ol 7. To a stirred solution of $NaNO_2$ (2 mmol) in water (0.5 mL) was added **6** (1 mmol) in 6 N HCl (0.5 mL) at 0 °C. After 10 min, the mixture was treated with a solution of 2-naphthol (1 mmol) in 10% NaOH (1 mL). [12b] The resultant red solid was stirred for about 0.5 h and filtered, washed with water, and dried and purified on silica gel column chromatography using hexane and ethyl acetate (49:1) as eluent. red solid; yield 63%; mp 189-190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 9.6 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33-7.29 (m, 5H), 7.25-7.23 (m, 3H), 7.21-7.18 (m, 2H), 7.13 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.8, 139.7, 137.9, 137.2, 136.5, 135.2, 133.1, 133.0, 132.3, 130.7, 130.3, 130.0, 129.7, 129.1, 128.6, 128.4, 128.2, 128.1, 127.4, 124.2, 122.2, 120.1, 99.1, 21.3; FT-IR (KBr) 3444, 3034, 2922, 2852, 1619, 1597, 1546, 1512, 1485, 1472, 1452, 1418, 1383, 1337, 1210, 1171, 1144, 1016, 813, 776, 730, 696 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{33}H_{25}N_3O$ 480.2076, found 480.2071.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, NMR (^{1}H, ^{13}C) spectra of the products. See DOI: 10.1039/b000000x/

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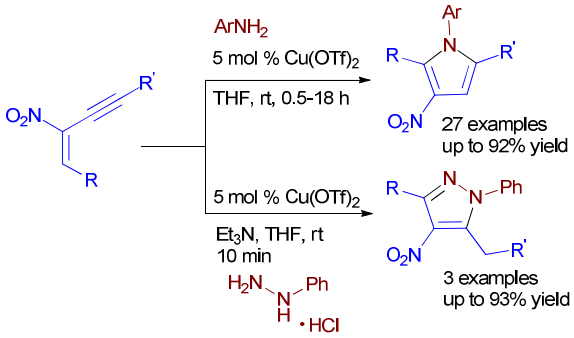
Table of Content



Various tetrasubstituted pyrroles/pyrazoles have been prepared from nitro-substituted 1,3-enynes with aromatic amines/hydrazines *via* a copper-catalyzed cascade aza-Michael addition, cyclization and aromatization at room temperature. This protocol is also effective for the synthesis of tetrasubstituted pyrazoles in high yields.