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Regioselective Synthesis of 1,3,4,5-Tetrasubstituted Pyrazoles from α-Alkenyl-α,β-Enones Derived from Morita-Baylis-Hillman Adducts

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Convenient synthetic method for 4-arylethylpyrazoles and 4-styrylpyrazoles was developed using α-alkenyl-α,β-enones readily accessed from the Morita-Baylis-Hillman reaction. For the synthesis of 4-arylethyl-pyrazole, the reactions with arylhydrazines needed to be carried out in *o*-dichlorobenzene under N_2 balloon atmosphere. On the other hand, 4-styrylpyrazoles required the reactions in ethanol under O_2 balloon atmosphere.

Key Words : Pyrazoles, α-Alkenyl-α,β-enones, Morita-Baylis-Hillman adducts, 1,3-H shift, Aerobic oxidation

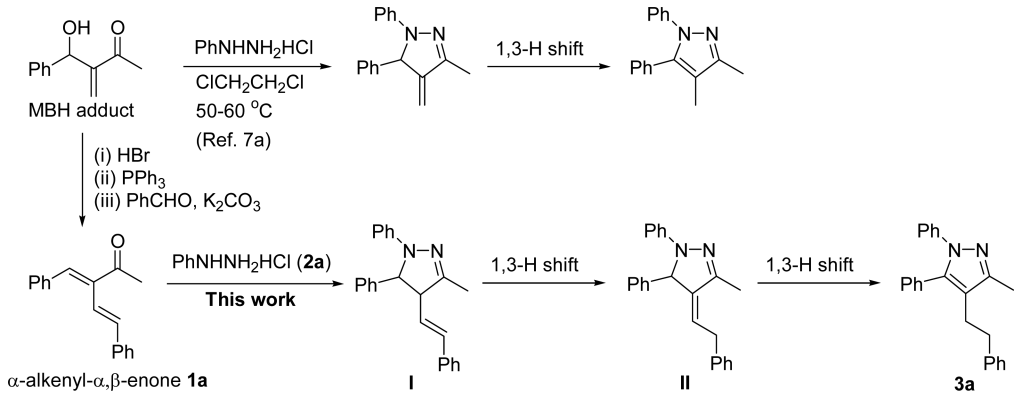
Introduction

1,3,4,5-Tetrasubstituted pyrazole derivatives are important synthetic targets due to their wide spectrum of biological activities.[1-5] Therefore, numerous methods have been reported for the synthesis of tetrasubstituted pyrazoles.[2-5] The condensation reaction between 1,3-dicarbonyl compounds and substituted hydrazines is the simplest synthetic method for pyrazoles.[2] The reaction of β-hydroxyketones or α,β-enones with substituted hydrazines provided pyrazolines, which could be oxidized to the corresponding pyrazoles in the presence of an oxidant such as MnO_2 or DDQ.[3] Besides these methods, numerous other synthetic approaches have been reported.[4,5]

Results and Discussion

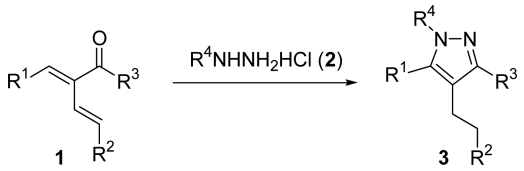
The Morita-Baylis-Hillman (MBH) adducts have been used for the synthesis of various heterocyclic compounds,[6] including pyrazoles.[7] In 2003, the first synthesis of poly-substituted pyrazoles from MBH adducts has been reported in our group, as shown in Scheme 1.[7a] The reaction of MBH adduct and substituted hydrazine provided 4-methylene-pyrazoline intermediate which was converted to 4-methyl-pyrazole by a rapid 1,3-H shift. During our recent studies using α-styryl-α,β-enones,[8] which was prepared from MBH bromide, we envisioned that the reaction of enone **1a** and phenylhydrazine could provide 4-styrylpyrazoline **I** and eventually 4-phenethylpyrazole **3a** *via* a double 1,3-H shift process (Scheme 1).[9]

The starting material **1a** was prepared from MBH adduct of methyl vinyl ketone *via* a simple two-step procedure, according to the reported method, namely a bromination and a Wittig reaction with benzaldehyde.[8] At the outset of our experiment, the reaction of **1a** and phenylhydrazine hydrochloride (**2a**) was carried out in refluxing $ClCH_2CH_2Cl$ for 30 h. 4-Phenethylpyrazole **3a** was obtained as expected; however, the yield of **3a** was low (28%). The reaction with phenylhydrazine or addition of an acid catalyst did not improve the yield of **3a**. The reaction in DMSO (80-90 °C) showed the formation of many intractable side products with low yield of **3a**. Thus we examined the reaction at higher temperature (130 °C) in *o*-dichlorobenzene (ODCB). To our delight, the yield of **3a** increased to 51% in short time (2 h). In the reaction, a trace amount of 4-styrylpyrazole **4a** (2%, *vide infra*) was also formed although the reaction was performed under N_2 balloon atmosphere. Compound **4a** must be formed *via* an aerobic oxidation of the intermediate



Scheme 1

Table 1. Synthesis of 4-arylethylpyrazoles[a]



Entry	1,3-Diene (**1**)	R^4NHNH_2HCl (**2**)	Product (%)
1	**1a** (R^1=Ph, R^2=Ph, R^3=Me)	**2a** (R^4=Ph)	**3a** (51)
2	**1a**	**2b** (R^4=*p*-ClPh)	**3b** (57)
3	**1a**	**2c** (R^4=$PhCH_2$)	**3c** (45)
4	**1b** (R^1=Ph, R^2=Ph, R^3=Et)	**2a**	**3d** (61)
5	**1c** (R^1=*p*-ClPh, R^2=Ph, R^3=Me)	**2a**	**3e** (48)
6	**1d** (R^1=Ph, R^2=*p*-PhPh, R^3=Me)	**2a**	**3f** (49)

[a]Conditions: **1** (0.5 mmol), **2** (1.2 equiv), ODCB, 130 °C, N_2 balloon, 2 h.

I or **3a**, by a trace amount of oxygen in the reaction mixture.[10] Actually, when we carried out the reaction under O_2 balloon atmosphere in ODCB, **4a** was obtained in an increased yield (29%) along with **3a** (17%).

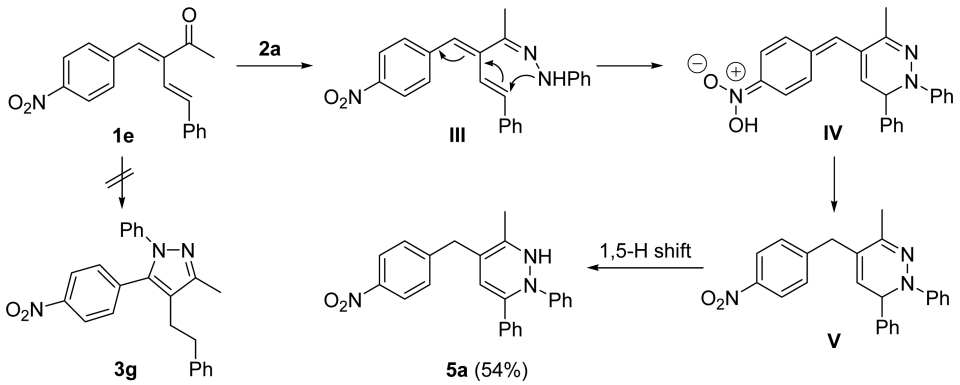
Encouraged by the promising results we carried out the synthesis of 4-arylethylpyrazoles **3b-f**, and the results are summarized in Table 1. The reactions of **1a** with *p*-chlorophenylhydrazine hydrochloride (**2b**) or benzylhydrazine hydrochloride (**2c**) afforded the corresponding pyrazoles **3b** and **3c** in moderate yields (entries 2 and 3). The reactions of **1b-d** with **2a** (entries 4-6) gave **3d-f** in moderate yields (48-61%).

However, when we carried out the reaction of 1,3-diene **1e**, bearing a *p*-nitrophenyl moiety, pyridazine derivative **5a** was obtained unexpectedly in moderate yield (54%) instead of the corresponding pyrazole **3g**, as shown in Scheme 2. The mechanism of the formation of pyridazine **5a** could be proposed as follows. The cyclization of hydrazone intermediate **III** might occur in a 6-*endo* mode,[11] presumably because of the electron-withdrawing nitro group. Subsequent proton-transfer processes produced a pyridazine **5a**.

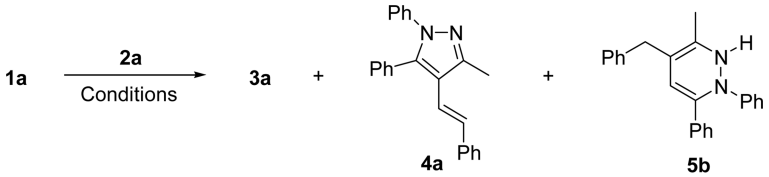
As described above, 4-styrylpyrazole **4a** was isolated in trace amount (2%) during the synthesis of 4-phenethylpyrazole **3a** in ODCB under N_2 balloon atmosphere. The yield of **4a** increased to 29% in ODCB under O_2 balloon atmosphere (*vide supra*). In order to prepare **4a** as a major product, we examined the reaction of **1a** and **2a** in ethanol under O_2 balloon atmosphere. As shown in Scheme 3 the yield of **4a** increased to 45%, and trace amount of **3a** (2%) was obtained along with pyridazine **5b** (7%). Increased yield of **4a** might be attributed to higher concentration of O_2 in EtOH solution than in ODCB. Compound **4a** could be converted to **3a** quantitatively (98%) under the usual catalytic hydrogenation conditions (Pd/C, EtOH, rt, H_2 balloon, 4 h).

Based on the successful result we synthesized 4-styrylpyrazole derivatives **4b-e**, as summarized in Table 2. The 4-styrylpyrazoles **4b-e** were isolated in moderate yields (37-51%). Trace amounts of the corresponding 4-arylethylpyrazoles and pyridazine derivatives were observed at the right positions on TLC; however, these compounds were not separated.

As a next entry, an alkenyl derivative **1h** was prepared and the reaction with **2a** was examined, as shown in Scheme 4. Compound **1h** was prepared from MBH acetate and 2-nitropropane *via* the sequential addition-elimination and

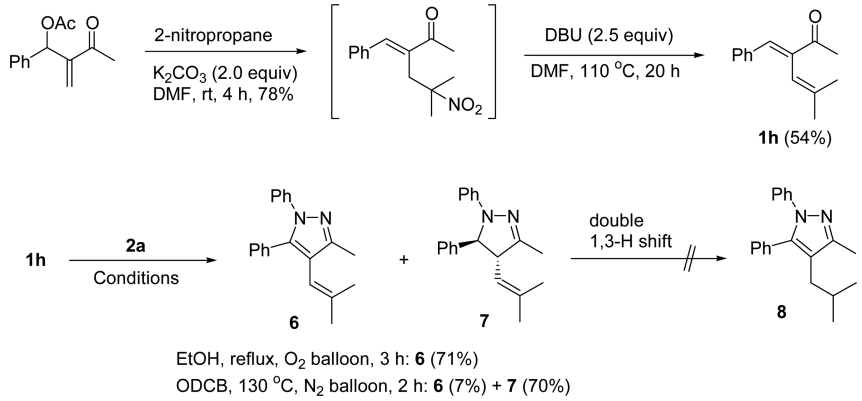


Scheme 2



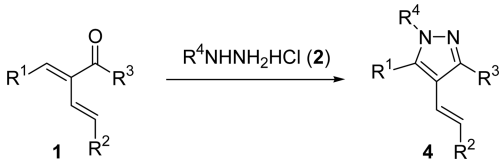
ODCB, 130 °C, O_2 balloon, 2 h: **3a** (17%) + **4a** (29%) + **5b** (< 5%)
EtOH, reflux, O_2 balloon, 3 h: **3a** (2%) + **4a** (45%) + **5b** (7%)

Scheme 3



Scheme 4

Table 2. Synthesis of 4-styrylpyrazoles[a]



Entry	1,3-Diene (**1**)	R^4NHNH_2HCl (**2**)	Product (%)
1	**1a**	**2a**	**4a** (45)
2	**1a**	**2d** (R^4=*p*-MeOPh)	**4b** (41)
3	**1a**	**2e** (R^4=*p*-NH_2SO_2Ph)	**4c** (37)
4	**1f** (R^1=*p*-MeOPh, R^2=Ph, R^3=Me)	**2a**	**4d** (50)
5	**1g** (R^1=Ph, R^2=*p*-MeOPh, R^3=Me)	**2b**	**4e** (51)

[a]Conditions: **1** (0.5 mmol), **2** (1.2 equiv), EtOH, reflux, O_2 balloon, 3 h.

DBU-mediated elimination of nitrous acid. The reaction of **1h** and **2a** in EtOH (O_2 balloon) afforded 4-isobutenylpyrazole **6** in good yield (71%) while the reaction in ODCB (N_2 balloon) produced 4-isobutenylpyrazoline **7** as a major product (70%). It is interesting to note that the formation of 4-isobutylpyrazole **8** was not observed, as for the conversion of **I** to **3a** (*vide supra*, Scheme 1).

In summary, we disclosed convenient syntheses of both 4-arylethylpyrazoles (ODCB, N_2 balloon) and 4-styrylpyrazoles (EtOH, O_2 balloon) by the reactions of arylhydrazines and α-alkenyl-α,β-enones, which were prepared from Morita-Baylis-Hillman adducts.

Experimental Section

Preparation of Starting Materials 1a-h. The starting materials **1a-g** were prepared according to the reported method,[8] and the spectroscopic data of **1a-h** are as follows.

Compound 1a: 81%; Pale yellow oil; IR (film) 1680, 1588, 1566, 1493, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 6.89 (dd, *J* = 16.5, 0.9 Hz, 1H), 6.98 (d, *J* = 16.5 Hz, 1H), 7.13-7.40 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 121.7, 126.6, 128.0, 128.5, 128.6, 128.8, 130.2, 135.3, 135.4, 137.2, 137.7, 138.5, 200.8; ESIMS *m/z* 271 (M^++Na).

Compound 1b: 74%; Pale yellow solid, mp 51-52 °C; IR (KBr) 1682, 1597, 1493, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.79 (q, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 16.5 Hz, 1H), 6.96 (dd, *J* = 16.5, 0.6 Hz, 1H), 7.15 (s, 1H), 7.16-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 33.8, 122.1, 126.6, 128.0, 128.5, 128.6 (2C), 130.2, 134.9, 135.6, 135.8, 137.2, 138.8, 204.4; ESIMS *m/z* 285 (M^++Na).

Compound 1c: 78%; Pale yellow solid, mp 52-53 °C; IR (KBr) 1680, 1585, 1490, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 6.83 (dd, *J* = 16.5, 1.2 Hz, 1H), 6.97 (d, *J* = 16.5 Hz, 1H), 7.16-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 122.2, 127.8, 128.6, 128.8, 129.0, 130.2, 133.6, 134.1, 135.3, 135.8, 138.1, 138.4, 200.6; ESIMS *m/z* 305 (M^++Na), 307 (M^++Na+2).

Compound 1d: 78%; Pale yellow solid, mp 98-99 °C; IR (KBr) 1677, 1596, 1486, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 6.93 (dd, *J* = 16.5, 1.2 Hz, 1H), 7.03 (d, *J* = 16.5 Hz, 1H), 7.22-7.41 (m, 11H), 7.46-7.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 121.8, 126.9, 127.1, 127.3, 127.4, 128.5, 128.8, 128.9, 130.3, 134.9, 135.5, 136.3, 137.7, 138.5, 140.5, 140.7, 200.9; ESIMS *m/z* 347 (M^++Na).

Compound 1e: 65%; Pale yellow solid, mp 108-109 °C; IR (KBr) 1682, 1591, 1516, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 6.83 (dd, *J* = 16.5, 1.2 Hz, 1H), 6.96 (d, *J* = 16.5 Hz, 1H), 7.15 (s, 1H), 7.20-7.34 (m, 5H), 7.54 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 120.5, 123.7, 126.8, 128.7, 128.8, 130.7, 133.3, 136.5, 137.3, 141.8, 142.1, 147.3, 200.7; ESIMS *m/z* 316 (M^++Na).

Compound 1f: 80%; Pale yellow solid, mp 77-78 °C; IR (KBr) 1672, 1603, 1508, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3H), 3.84 (s, 3H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.96 (dd, *J* = 16.8, 1.2 Hz, 1H), 7.06 (d, *J* = 16.8 Hz, 1H), 7.23-7.36 (m, 5H), 7.40-7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 55.3, 114.0, 122.3, 126.5, 127.8, 128.0, 128.6, 132.1, 135.0, 136.5, 137.4, 138.2, 160.2, 200.5; ESIMS *m/z* 301 (M^++Na).

Compound 1g: 61%; Pale yellow oil; IR (film) 1699, 1605, 1510, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51

(s, 3H), 3.80 (s, 3H), 6.85 (dd, J = 16.5, 0.9 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 16.5 Hz, 1H), 7.25 (s, 1H), 7.32-7.48 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 55.3, 114.1, 119.7, 127.9, 128.4, 128.6, 130.0, 130.2, 134.8, 135.6, 136.6, 138.9, 159.6, 201.2; ESIMS *m/z* 301 (M^++Na).

Compound 1h: 54%; Pale yellow oil; IR (film) 1676, 1591, 1491, 1447, 1352 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (d, J = 0.9 Hz, 3H), 1.88 (d, J = 1.2 Hz, 3H), 2.36 (s, 3H), 5.97-6.00 (m, 1H), 7.29-7.37 (m, 4H), 7.54-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 25.5, 27.6, 119.9, 128.3, 128.9, 130.3, 135.7, 137.6, 137.8, 138.8, 200.7; ESIMS *m/z* 223 (M^++Na).

Typical Procedure for the Synthesis of 3a. A stirred mixture of **1a** (124 mg, 0.5 mmol) and **2a** (87 mg, 0.6 mmol) in ODCB (1.5 mL) was heated to 130 °C for 2 h under N_2 balloon atmosphere. After the usual extractive workup and column chromatographic purification process (hexanes/Et_2O, 20:1), compound **3a** was isolated as colorless oil (87 mg, 51%) along with **4a** as a white solid (4 mg, 2%). Other 4-arylethylpyrazoles **3b-f** were synthesized similarly, and the spectroscopic data of **3a-f** and **5a** are as follows.

Compound 3a: 51%; Colorless oil; IR (film) 1599, 1504, 1452, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 2.62-2.69 (m, 4H), 6.95-7.00 (m, 4H), 7.05-7.24 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 25.7, 36.9, 118.7, 124.4, 125.9, 126.3, 128.0, 128.3, 128.4, 128.5, 128.6, 129.7, 130.9, 140.1, 140.7, 141.6, 148.4; ESIMS *m/z* 339 (M^++H). Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.32; H, 6.79; N, 8.13.

Compound 3b: 57%; Pale yellow oil; IR (film) 1595, 1495, 1452, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 2.60-2.68 (m, 4H), 6.92-6.98 (m, 4H), 7.03 (d, J = 9.0 Hz, 2H), 7.08-7.18 (m, 5H), 7.21-7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 25.6, 36.8, 119.1, 125.3, 126.0, 128.3 (2C), 128.5, 128.6, 128.7, 129.7, 130.6, 131.8, 138.6, 140.7, 141.4, 148.8; ESIMS *m/z* 373 (M^++H), 375 (M^++H+2). Anal. Calcd for $C_{24}H_{21}ClN_2$: C, 77.30; H, 5.68; N, 7.51. Found: C, 77.37; H, 5.81; N, 7.36.

Compound 3c: 45%; Pale yellow oil; IR (film) 1603, 1495, 1452, 1377 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.51-2.64 (m, 4H), 5.03 (s, 2H), 6.83-6.92 (m, 6H), 7.07-7.27 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 25.6, 36.8, 52.7, 116.9, 125.8, 126.7, 127.2, 128.2, 128.3, 128.38, 128.40, 128.6, 129.8, 130.6, 138.1, 141.6, 142.1, 146.9; ESIMS *m/z* 353 (M^++H).

Compound 3d: 61%; Colorless oil; IR (film) 1597, 1504, 1452, 1443, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, J = 7.8 Hz, 3H), 2.72 (q, J = 7.8 Hz, 2H), 2.73 (app s, 4H), 7.03-7.08 (m, 4H), 7.12-7.25 (m, 8H), 7.27-7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 20.1, 25.6, 37.2, 118.1, 124.4, 125.9, 126.2, 128.0, 128.2, 128.4 (2C), 128.5, 129.7, 131.1, 140.1, 140.5, 141.6, 153.5; ESIMS *m/z* 353 (M^++H).

Compound 3e: 48%; Pale yellow oil; IR (film) 1597, 1504, 1493, 1452, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 2.58-2.71 (m, 4H), 6.80 (d, J = 8.4 Hz, 2H), 6.94-6.97 (m, 2H), 7.05-7.19 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 25.6, 36.7, 118.8, 124.4, 126.0, 126.6, 128.3, 128.5, 128.66, 128.71, 129.3, 131.0, 134.1, 139.4, 139.8, 141.3, 148.5; ESIMS *m/z* 373 (M^++H), 375 (M^++H+2).

Compound 3f: 49%; Pale yellow oil; IR (film) 1599, 1504, 1485, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 2.74-2.81 (m, 4H), 7.02-7.05 (m, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.15-7.34 (m, 9H), 7.40 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 25.6, 36.4, 118.6, 124.4, 126.3, 126.93, 126.96, 127.0, 128.0, 128.4, 128.6, 128.7, 128.9, 129.7, 130.9, 138.9, 140.1, 140.6, 140.7, 141.0, 148.4; ESIMS *m/z* 415 (M^++H). Anal. Calcd for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.68; H, 6.54; N, 6.68.

Compound 5a: 54%; Pale yellow solid, mp 136-138 °C; IR (KBr) 3352, 1603, 1516, 1497, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (s, 3H), 3.83 (s, 2H), 6.04 (s, 1H), 6.37-6.40 (m, 3H), 6.76-6.82 (m, 1H), 7.05-7.18 (m, 5H), 7.28-7.34 (m, 4H), 8.06 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.3, 32.7, 107.0, 112.2, 115.8, 120.7, 123.6, 126.5, 127.3, 127.9, 128.3, 129.1, 129.5, 131.8, 132.9, 146.2, 147.6, 149.9; ESIMS *m/z* 384 (M^++H). Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.43; H, 5.47; N, 10.78.

Typical Procedure for the Synthesis of 4a. A stirred mixture of **1a** (124 mg, 0.5 mmol) and **2a** (87 mg, 0.6 mmol) in EtOH (1.5 mL) was heated to reflux for 3 h under O_2 balloon atmosphere. After the usual extractive workup and column chromatographic purification process (hexanes/Et_2O, 20:1), compound **4a** was isolated as a white solid (76 mg, 45%) along with **3a** (4 mg, 2%) and **5b** (12 mg, 7%). Other 4-styrylpyrazoles **4b-e** were synthesized similarly, and the spectroscopic data of **4a-e**, **5b**, **6** and **7** are as follows.

Compound 4a: 45%; White solid, mp 127-128 °C; IR (KBr) 1597, 1504, 1427, 1379 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H), 6.71 (d, J = 16.5 Hz, 1H), 6.83 (d, J = 16.5 Hz, 1H), 7.09-7.25 (m, 10H), 7.27-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 117.5, 119.8, 124.7, 125.9, 126.9, 127.0, 128.3, 128.5, 128.55, 128.57, 128.7, 130.1, 130.3, 138.1, 139.7, 141.2, 147.6; ESIMS *m/z* 337 (M^++H). Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.59; H, 6.17; N, 8.19.

Compound 4b: 41%; Pale yellow solid, mp 130-131 °C; IR (KBr) 1638, 1516, 1462, 1447, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 3.77 (s, 3H), 6.76 (d, J = 16.5 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 16.5 Hz, 1H), 7.13 (d, J = 9.0 Hz, 2H), 7.18-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 55.4, 113.9, 117.0, 119.9, 125.9, 126.2, 126.9, 128.1, 128.4, 128.52, 128.54, 130.2, 130.3, 133.0, 138.2, 141.2, 147.2, 158.4; ESIMS *m/z* 367 (M^++H).

Compound 4c: 37%; Pale yellow solid, mp 243-244 °C; IR (KBr) 3424, 1647, 1595, 1333, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 2.58 (s, 3H), 6.73 (br s, 2H), 6.76 (d, J = 16.5 Hz, 1H), 6.85 (d, J = 16.5 Hz, 1H), 7.17-7.22 (m, 1H), 7.24-7.36 (m, 8H), 7.42-7.45 (m, 3H), 7.80 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 13.9, 118.0, 118.6, 123.3, 125.3, 126.3, 126.6, 128.0, 128.3, 128.4, 128.5, 129.2, 129.6, 137.2, 140.6, 140.8, 141.6, 147.91; ESIMS *m/z* 416 (M^++H).

Compound 4d: 50%; Pale yellow solid, mp 125-126 ºC; IR (KBr) 1597, 1512, 1501, 1431, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 3.82 (s, 3H), 6.78 (d, *J* = 16.5 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 16.5 Hz, 1H), 7.13-7.38 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 55.2, 114.0, 117.3, 120.0, 122.3, 124.7, 125.9, 126.8, 126.9, 128.0, 128.6, 128.7, 131.5, 138.2, 139.8, 141.1, 147.6, 159.6; ESIMS *m/z* 367 (M^++H).

Compound 4e: 51%; Pale yellow solid, mp 135-136 ºC; IR (KBr) 1605, 1506, 1464, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 3.80 (s, 3H), 6.73 (app s, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.20-7.25 (m, 4H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.36-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 55.3, 114.0, 117.4, 118.1, 125.6, 127.1, 128.2, 128.6, 128.73, 128.9, 130.0, 130.2, 130.8, 132.3, 138.3, 140.8, 147.9, 158.9; ESIMS *m/z* 401 (M^++H), 403 (M^++H+2). Anal. Calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99. Found: C, 75.07; H, 5.44; N, 6.78.

Compound 5b: 7%; Pale yellow oil; IR (film) 3350, 1601, 1495, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 3.83 (s, 2H), 6.16 (s, 1H), 6.44 (s, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.83-6.89 (m, 1H), 7.11-7.32 (m, 10H), 7.40 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.4, 32.7, 107.4, 112.3, 117.6, 120.6, 125.7, 126.2, 127.3, 127.6, 128.2, 128.3, 128.4, 129.4, 132.1, 132.4, 141.9, 147.8; ESIMS *m/z* 339 (M^++H).

Compound 6: 71%; Pale yellow oil; IR (film) 1599, 1504, 1445, 1375, 1364 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 1.2 Hz, 3H), 2.27 (s, 3H), 5.86-5.89 (m, 1H), 7.13-7.17 (m, 2H), 7.20-7.30 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.7, 20.0, 25.5, 114.9, 118.3, 124.9, 126.6, 127.7, 128.2, 128.7, 129.6, 131.1, 137.7, 140.0, 140.2, 148.6; ESIMS *m/z* 289 (M^++H). Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.21; H, 7.23; N, 9.65.

Compound 7: 70%; Pale yellow oil; IR (film) 1599, 1499, 1452, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, *J* = 1.5 Hz, 3H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.95 (d, *J* = 1.2 Hz, 3H), 3.68-3.75 (m, 1H), 4.56 (d, *J* = 9.0 Hz, 1H), 5.13-5.19 (m, 1H), 6.72-6.77 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 7.10-7.16 (m, 2H), 7.24-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 18.2, 25.8, 60.0, 72.2, 113.5, 118.9, 121.7, 125.8, 127.3, 128.8, 128.9, 136.4, 142.2, 146.4, 151.2; ESIMS *m/z* 291 (M^++H).

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