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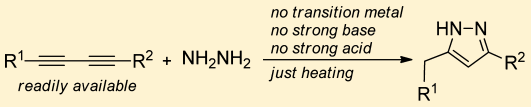
Synthesis of 3,5-Disubstituted Pyrazoles via Cope-Type Hydroamination of 1,3-Dialkynes

Liangguang Wang, Xiaoqiang Yu,* Xiujuan Feng, and Ming Bao*

State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116023, China

Supporting Information

ABSTRACT: An efficient method for the synthesis of 3,5-disubstituted pyrazoles is described. The reactions of 1,3-dialkynes with hydrazine proceeded smoothly in dimethyl sulfoxide under mild reaction conditions to produce 3,5-disubstituted pyrazoles in satisfactory to excellent yields. A one-pot procedure of the transformation has been developed.



Pyrazoles represent an interesting structural motif found frequently in various bioactive molecules.[1] Over the past years, many methods have been developed for the construction of the pyrazole nucleus, including the [3 + 2] cycloaddition of alkenes/alkynes with 1,3-dipoles (diazoalkanes and nitrile imines),[2] the reaction of hydrazine with a three-carbon atom component (such as 1,3-dicarbonyl compound, α,β-unsaturated carbonyl compound),[3] the gold-catalyzed addition of phenylhydrazine to a 1,3-dialkyne,[4] and others.[5] Although mono- and polysubstituted-pyrazoles can be obtained using these methods, the synthesis frequently suffers from drawbacks, such as multistep reactions, harsh reaction conditions (strong bases or strong mineral acids are often required, or prolonged heating to high temperature is necessary), and the use of transition-metal catalysts or special starting materials.

Beauchemin and co-workers have reported the uncatalyzed intermolecular Cope-type hydroamination reaction of alkynes (or alkenes) with hydroxylamine (or hydrazine) in 2008.[6] Recently, we have reported that 3,5-disubstituted isoxazoles can be readily obtained from the reaction of 1,3-dialkynes with hydroxylamine (NH_2OH); this reaction proceeded smoothly in dimethyl sulfoxide (DMSO) under transition metal-, strong base-, and strong acid-free conditions.[7] The success in achieving cycloaddition of 1,3-dialkynes with hydroxylamine encouraged us to examine the cycloaddition of 1,3-dialkynes with hydrazine (NH_2NH_2) under the same reaction conditions. As expected, the cycloaddition of 1,3-dialkynes with hydrazine took place to offer 3,5-disubstituted pyrazoles (Scheme 1). The intermolecular Cope-type hydroamination reaction of 1,3-dialkynes **1** with hydrazine occurred during heating to produce intermediate **A** upon a proton-transfer process.[8] The isomerization of **A** subsequently took place to produce an allenyl oxime intermediate **B**, which then transformed into a 3,5-disubstituted pyrazoles **2** via intramolecular electrophilic addition. The results are reported in the current work.

In our initial studies, the reaction of 1,4-diphenylbuta-1,3-diyne (**1a**) with hydrazine was chosen as a model to optimize the reaction conditions. The results are shown in Table 1. The reaction of **1a** with hydrazine was initially performed under the same reaction conditions as employed in the reaction of **1a** with hydroxylamine (in DMSO at 110 °C for 20 h).[7] The desired

Scheme 1. Synthesis of 3,5-Disubstituted Pyrazoles via Cope-Type Hydroamination of 1,3-Dialkynes

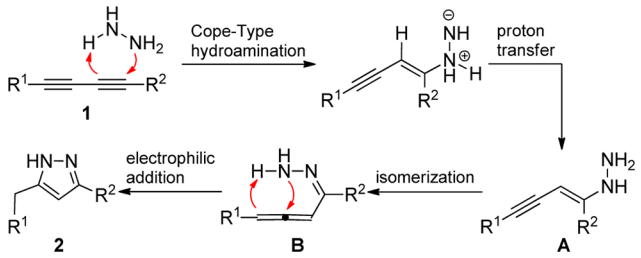
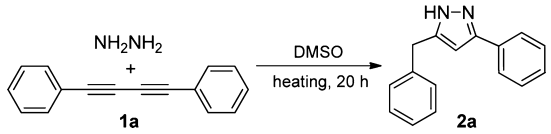


Table 1. Reaction Conditions Screening[a]



entry	temp (°C)	NH_2NH_2 (equiv)	yield (%)
1	110	4.0	83
2	100	4.0	84
3	90	4.0	83
4	80	4.0	83
5	70	4.0	82
6	60	4.0	83
7	50	4.0	68
8	60	3.5	82
9	60	3.0	83
10	60	2.5	74

[a]Reaction conditions: 1,4-diphenylbuta-1,3-diyne (**1a**, 0.4 mmol, 81.0 mg) and aqueous hydrazine solution (50 wt %, 2.5−4.0 equiv), and DMSO (3.0 mL) in sealed tube for 20 h.

3,5-disubstituted pyrazole, 5-benzyl-3-phenylpyrazole (**2a**), was obtained in 83% yield (entry 1). The results obtained from the subsequent investigations on the reaction temperature indicated that the reaction temperature can be reduced to 60

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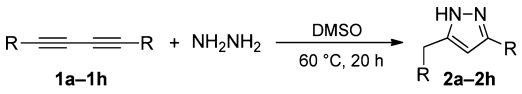
°C (entries 2–7). To facilitate the complete transformation of the 1,3-dialkyne substrate **1a** to product, an excess of hydrazine was used. The results indicated that the use of 3.0 equiv of hydrazine is necessary to obtain product **2a** in good yield (83%; entry 9 vs entries 6, 8, and 10). Therefore, the subsequent reactions of the symmetric (**1a–1h**) and unsymmetric (**3a–3j**) 1,3-dialkynes with hydrazine (3.0 equiv) were performed in DMSO at 60 °C for 20 h.

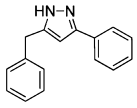
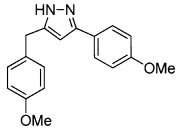
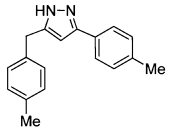
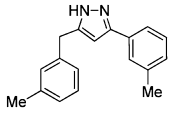
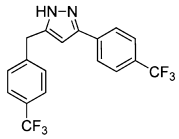
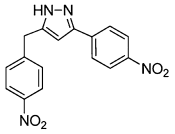
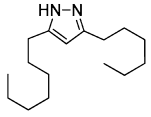
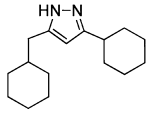
The reactions of symmetric 1,3-dialkynes **1a–1h** with hydrazine were performed under optimized conditions, and the results are summarized in Table 2. 3,5-Disubstituted pyrazole **2a–2f** were obtained from the reactions of aromatic 1,3-dialkynes **1a–1f** in good to excellent yields (entries 1–6, 76–93%). The formation of 3,5-disubstituted pyrazole in relatively higher yield from a 1,3-dialkyne bearing an electron-withdrawing group on benzene ring than those from a 1,3-dialkyne bearing an electron-donating group on benzene ring was observed (entries 5 and 6 vs entries 1–4). This result suggests that 1,3-dialkynes can be activated by decreasing their electron density. The aliphatic 1,3-dialkynes **1g** and **1h** were also employed successfully in the synthesis of 3,5-disubstituted pyrazoles. The corresponding products **2g** and **2h** were obtained in 60 and 76% yields, respectively (entries 7 and 8). The reaction of **1a** with phenylhydrazine was finally tested under optimized conditions. No reaction was observed.

The successful acquisition of 3,5-disubstituted pyrazoles from the reaction of symmetric 1,3-dialkynes with hydrazine encouraged the current authors to examine the reaction of unsymmetric 1,3-dialkynes with hydrazine. The results are summarized in Table 3. The reactions of unsymmetric 1,3-dialkynes **3a** and **3b** having the same 4-methoxyphenyl group with hydrazine proceeded smoothly to produce a mixture of two products, which can be separated with chromatography (entry 1: **4a**, 41% yield; **5a**, 32% yield. entry 2: **4b**, 72% yield; **5b**, 9% yield). Similar results were obtained when 1,3-dialkynes **3c** and **3d** having the same 4-methylphenyl group were employed as substrates. Products **4c**, **5c**, **4d**, and **5d** were isolated in 61, 12, 64, and 12% yields, respectively (entries 3 and 4). The use of unsymmetric 1,3-dialkynes **3e–3h** having the same 4-nitrophenyl group led to the selective formation of 3,5-disubstituted pyrazoles **4e–4h** in good to excellent yields (entries 5–8, 87–94%). 3,5-Disubstituted pyrazoles **4i** and **4j**

Table 2. Synthesis of 3,5-Disubstituted Pyrazoles from Symmetric 1,3-Dialkynes[a]

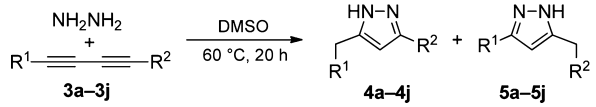


1a–1h **2a–2h**

entry	R		product **2**		yield (%)
1	Ph	**1a**		**2a**	83
2	4-MeOC$_6$H$_4$	**1b**		**2b**	76
3	4-MeC$_6$H$_4$	**1c**		**2c**	78
4	3-MeC$_6$H$_4$	**1d**		**2d**	78
5	4-CF$_3$C$_6$H$_4$	**1e**		**2e**	93
6	4-NO$_2$C$_6$H$_4$	**1f**		**2f**	93
7	*n*-Hexyl	**1g**		**2g**	60[b]
8	*c*-Hexyl	**1h**		**2h**	76

[a]Reaction conditions: symmetric 1,3-dialkyne (**1a–1h**, 0.4 mmol), aqueous hydrazine solution (50 wt %, 3.0 equiv, 76.9 mg), and DMSO (3.0 mL) in sealed tube at 60 °C for 20 h. [b]1,3-Dialkyne **1g** was recovered in 26% yield.

Table 3. Synthesis of 3,5-Disubstituted Pyrazoles from Unsymmetric 1,3-Dialkynes[a]



3a–3j **4a–4j** **5a–5j**

entry	alkyne **3**	yield of **4** (%)	yield of **5** (%)
1	**3a**, R^1 = Ph, R^2 = 4-MeOC$_6$H$_4$	**4a**, 41	**5a**, 32
2	**3b**, R^1 = 4-FC$_6$H$_4$, R^2 = 4-MeOC$_6$H$_4$	**4b**, 72	**5b**, 9
3	**3c**, R^1 = 4-MeC$_6$H$_4$, R^2 = *n*-Hexyl	**4c**, 61	**5c**, 12
4	**3d**, R^1 = 4-MeC$_6$H$_4$, R^2 = *c*-Hexyl	**4d**, 64	**5d**, 12
5	**3e**, R^1 = 4-NO$_2$C$_6$H$_4$, R^2 = 4-MeOC$_6$H$_4$	**4e**, 87	**5e**, 0
6	**3f**, R^1 = 4-NO$_2$C$_6$H$_4$, R^2 = Ph	**4f**, 90	**5f**, 0
7	**3g**, R^1 = 4-NO$_2$C$_6$H$_4$, R^2 = *n*-Hexyl	**4g**, 89	**5g**, 0
8	**3h**, R^1 = 4-NO$_2$C$_6$H$_4$, R^2 = *c*-Hexyl	**4h**, 94	**5h**, 0
9	**3i**, R^1 = Ph, R^2 = *n*-Hexyl	**4i**, 78	**5i**, 0
10	**3j**, R^1 = Ph, R^2 = *c*-Hexyl	**4j**, 81	**5j**, 0

[a]Reaction conditions: unsymmetric 1,3-dialkyne (**3a–3j**, 0.4 mmol), aqueous hydrazine solution (50 wt %, 3.0 equiv, 76.9 mg), and DMSO (3.0 mL) in sealed tube at 60 °C for 20 h.

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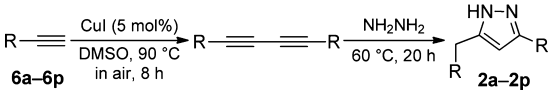
were also obtained as a sole product from the reaction of unsymmetric 1,3-dialkyne **3i** or **3j** with hydrazine (entry 9: **4i**, 78% yield; entry 10: **4j**, 81% yield). These results obtained indicated that the reaction selectivity was controlled by the electron property of substituents R^1 and R^2 in 1,3-dialkynes; the Cope-type hydroamination of 1,3-dialkynes with hydrazine facilely took place on the triplet bond bearing an electron-donating group to produce 3,5-disubstituted pyrazoles **4**.

Finally, the one-pot synthesis of 3,5-disubstituted pyrazoles from alkynes was examined, and the results are summarized in Table 4. After the Cu-catalyzed homocoupling reaction of alkyne was completed,[9] aqueous hydrazine solution was added to the resultant mixture. The reaction mixture was then treated at 60 °C for 20 h. A similar yield of **2a** was observed in the reaction of phenylacetylene (**6a**) (entry 1, 82%). The reactions of arylacetylenes **6b**–**6d** and **6i** bearing an electron-donating group (MeO, Me, ^{n}Bu) on 4- or 3-position of benzene ring produced the desired products **2b**–**2d** and **2i** in good yields (entries 2–4 and 9, 76–78%). However, the reaction of 2-methyl phenylacetylene (**6j**) produced 3,5-disubstituted pyrazole **2j** in low yield (entry 10, 60%). The poor reactivity of **6j** was considered to be due to the steric effect of the 2-methyl group in alkyne substrate. The relatively high yields were also observed in the reactions of arylacetylenes **6e**, **6f**, and **6k**–**6m** bearing an electron-withdrawing group on benzene ring. The desired products, 3,5-disubstituted pyrazoles **2e**, **2f**, and **2k**–**2m**, were isolated in the range of 86–92% yields (entries 5, 6, and 11–13). The aliphatic alkynes **6g** and **6h** were also utilized successfully for the synthesis of 3,5-disubstituted pyrazoles. Products **2g** and **2h** were obtained in 60 and 76% yields, respectively (entries 7 and 8). Finally, the reactions of 1-naphthylacetylene (**6n**), 3-pyridinylacetylene (**6o**), and 3-thienylacetylene (**6p**) were investigated under the same conditions. The corresponding products **2n**–**2p** were obtained in moderate to excellent yields (entries 14–16, 60, 80, and 78%, respectively). All the new products **2b**–**2p**, **4a**–**4j**, **and 5a**–**5d** were identified through their NMR and HRMS data as well as IR spectra.[10]

To prove the practicality of the present method in the synthesis of 3,5-disubstituted pyrazoles, a gram-scale synthesis of the 3,5-disubstituted pyrazole **2a** was performed, and the result is shown in Scheme 2. When 1.01 g of **1a** was utilized, 1.01 g of product **2a** was obtained in 86% yield.

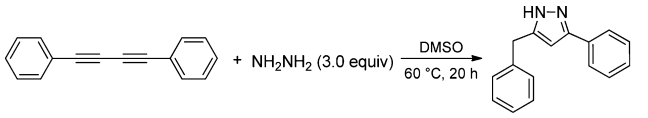
Table 4. One-Pot Synthesis of 3,5-Disubstituted Pyazoles from Alkynes[a,b]



entry	alkyne **6**	product **2**	yield (%)
1	**6a**, R = Ph	**2a**	82
2	**6b**, R = 4-$MeOC_6H_4$	**2b**	76
3	**6c**, R = 4-MeC_6H_4	**2c**	78
4	**6d**, R = 3-MeC_6H_4	**2d**	78
5	**6e**, R = 4-$CF_3C_6H_4$	**2e**	91
6	**6f**, R = 4-$NO_2C_6H_4$	**2f**	92
7	**6g**, R = *n*-Hexyl	**2g**	60[c]
8	**6h**, R = *c*-Hexyl	**2h**	76
9	**6i**, R = 4-^{n}Bu	**2i**	78
10	**6j**, R = 2-MeC_6H_4	**2j**	65[d]
11	**6k**, R = 4-BrC_6H_4	**2k**	86
12	**6l**, R = 4-FC_6H_4	**2l**	88
13	**6m**, R = 3,4-$F_2C_6H_4$	**2m**	86
14	**6n**, R = 1-Naphthyl	**2n**	60[e]
15	**6o**, R = 3-Pyridyl	**2o**	80
16	**6p**, R = 3-Thienyl	**2p**	78

[a]Reaction conditions for first step: alkyne (**6a**–**6p**, 0.6 mmol) and CuCl (5 mol %, 3.0 mg) in DMSO (3.0 mL) at 90 °C in air for 8 h. [b]Reaction conditions for second step: aqueous hydrazine solution (50 wt %, 1.5 equiv, 57.7 mg) in sealed tube at 60 °C for 20 h. [c]1,3-Dialkyne **1g** was recovered in 21% yield. [d]1,3-Dialkyne **1j** was recovered in 20% yield. [e]1,3-Dialkyne **1n** was recovered in 25% yield.

Scheme 2. Gram-Scale Synthesis of the 3,5-Disubstituted Pyrazole 2a



In summary, a novel and general method for the synthesis of 3,5-disubstituted pyrazoles was developed using simple and readily available starting materials, namely, 1,3-dialkynes/alkynes and aqueous hydrazine solution. The intermolecular Cope-type hydroamination reaction of 1,3-dialkynes with hydrazine and the subsequent electrophilic addition proceeded smoothly under transition metal-, strong base-, and strong acid-free conditions to produce 3,5-disubstituted pyrazoles in satisfactory to excellent yields. The wide availability of the starting materials, mild reaction conditions, and experimental simplicity should make the present methodology more useful in organic synthesis.

EXPERIMENTAL SECTION

General Methods. Solvents were dried and degassed before use by standard procedures. NMR spectra were run in $CDCl_3$ on a 400 MHz instrument and recorded at the following frequencies: proton (^{1}H, 400 MHz), carbon (^{13}C, 100 MHz). IR spectra were recorded on a FT-IR spectrometer. High resolution mass spectra were recorded on either a Q-TOF mass spectrometer or a GC-TOF mass spectrometer. The starting materials **6a**–**6p** are commercially available. The starting materials **1a**–**1h** and **3a**–**3i** have appeared in the literature.[7,11−17]

Preparation and Characterization of Starting Material 3j. A reaction flask was charged with a mixture of CuI (38.4 mg, 0.2 mmol), P(*o*-Tol)$_3$ (121.6 mg, 0.4 mmol), K_2CO_3 (552.0 mg, 4.0 mmol), ethynylcyclohexane (216.4 mg, 2.0 mmol), and 1-(bromoethynyl)-4-methylbenzene, prepared following literature procedure[18] (507.2 mg, 2.6 mmol), and anhydrous ethanol (EtOH, 10.0 mL). The reaction mixture was stirred at 100 °C for 12 h and then was cooled to room temperature. The resultant mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: cyclohexane) to afford 1-(cyclohexylbuta-1,3-diyn-1-yl)-4-methylbenzene (**3j**). Yield: 80%, 355.7 mg, white solid, mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 2.56–2.51 (m, 1H), 2.33 (s, 3H), 1.84–1.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.5, 129.3, 119.2, 88.3, 75.7, 73.9, 65.3, 32.4, 29.9, 25.9, 24.9, 21.7; IR (KBr) 2937, 2854, 2235, 2141, 1916, 1507, 1466, 820 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{18}$ 222.1413 [M]$^+$, found 222.1409.

General Procedure for Synthesis of 3,5-Disubstituted Pyrazoles from Symmetric 1,3-Dialkynes. A reaction flask was charged with a mixture of symmetric 1,3-dialkyne (**1**, 0.4 mmol),

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aqueous hydrazine solution (50 wt %, 3.0 equiv, 76.9 mg), and DMSO (3.0 mL). The reaction mixture was sealed and stirred at 60 °C for 20 h and then was cooled to room temperature. Water (10 mL) was added to the resultant mixture. The product was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were washed with brine (10 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 20:1) to afford 3,5-disubstituted pyrazoles **2**.

5-Benzyl-3-phenyl-1*H*-pyrazole (2a).[19] Yield: 83%, 77.9 mg, white solid, mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.2 Hz, 2H), 7.38−7.24 (m, 8H), 6.35 (s, 1H), 4.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 132.1, 128.9, 128.8, 128.1, 126.8, 125.8, 102.2, 33.3; IR (KBr) 3185, 3131, 3046, 3025, 2912, 1949, 1604, 1570, 1494, 1464, 1453, 764, 721 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{14}N_2$ 234.1157 [M]$^+$, found 234.1164.

5-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (2b). Yield: 76%, 89.5 mg, white solid, mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.87−6.82 (m, 4H), 6.23 (s, 1H), 3.92 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 158.4, 149.1, 148.0, 130.8, 129.9, 127.0, 124.9, 114.25, 114.19, 101.4, 55.4, 32.5; IR (KBr) 3445, 3246, 3009, 2957, 2838, 1895, 1613, 1525, 1513, 1438, 1282, 1250, 1030, 838, 796 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}N_2O_2$ 294.1368 [M]$^+$, found 294.1363.

5-(4-Methylbenzyl)-3-(*p*-tolyl)-1*H*-pyrazole (2c). Yield: 78%, 81.9 mg, white solid, mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.13−7.07 (m, 6H), 6.29 (s, 1H), 3.92 (s, 2H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.09, 136.08, 135.6, 135.5, 129.4, 129.3, 128.7, 125.6, 32.8, 21.3, 21.1; IR (KBr) 3227, 3018, 2917, 2859, 1900, 1639, 1580, 1566, 1513, 1445, 1112, 961, 787 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}N_2$ 262.1470 [M]$^+$, found 262.1461.

5-(3-Methylbenzyl)-3-(*m*-tolyl)-1*H*-pyrazole (2d). Yield: 78%, 81.9 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.48 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.21−7.13 (m, 2H), 7.07−7.00 (m, 4H), 6.23 (s, 1H), 3.90 (s, 2H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.34, 138.26, 129.6, 128.7, 128.6, 128.5, 127.3, 126.4, 125.8, 122.8, 33.2, 21.41, 21.40; IR (neat) 3175, 3102, 3018, 2918, 1608, 1589, 1573, 1476, 1025, 758 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}N_2$ 262.1470 [M]$^+$, found 262.1473.

5-(4-(Trifluoromethyl)benzyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (2e). Yield: 93%, 137.7 mg, white solid, mp 174−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 6.40 (s, 1H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 135.7, 130.7 (q, ^2J = 32.6 Hz), 130.1 (q, ^2J = 32.6 Hz), 129.6, 129.2, 128.4, 126.2, 126.0, 124.3 (q, ^1J = 270.1 Hz), 103.1, 33.0; IR (KBr) 2918, 1619, 1508, 1459, 1436, 1417, 1331, 1160, 1111, 1069, 841 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{12}N_2F_6$ 370.0905 [M]$^+$, found 370.0896.

5-(4-Nitrobenzyl)-3-(4-nitrophenyl)-1*H*-pyrazole (2f). Yield: 93%, 120.6 mg, pale yellow solid, mp 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.2 (s, 1H), 8.25 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 4.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 152.2, 151.7, 148.0, 145.5, 135.2, 135.1, 131.1, 129.5, 129.1, 108.2, 36.2; IR (KBr) 3113, 3074, 3010, 1636, 1602, 1512, 1349, 1109, 963, 855 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}N_4O_4$ 324.0859 [M]$^+$, found 324.0867.

5-Heptyl-3-hexyl-1*H*-pyrazole (2g). Yield: 60%, 60.1 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 5.85 (s, 1H), 2.60 (t, J = 7.6 Hz, 4H), 1.62−1.59 (m, 4H), 1.30−1.27 (m, 14H), 0.88 (t, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 102.0, 31.9, 31.8, 29.64, 29.60, 29.5, 29.3, 27.3, 22.8, 22.7, 14.2; IR (neat) 3191, 3132, 3102, 3027, 2955, 2927, 2856, 1580, 1466 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{30}N_2$ 250.2409 [M]$^+$, found 250.2405.

3-Cyclohexyl-5-(cyclohexylmethyl)-1*H*-pyrazole (2h). Yield: 76%, 74.9 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 5.81 (s, 1H), 2.63−2.59 (m, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.99−0.88 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 147.7, 101.1, 38.4, 36.6, 35.2, 33.4, 33.2, 26.6, 26.42, 26.36, 26.2; IR (neat) 3196, 3103, 3022, 2924, 2851, 1681, 1575, 1448 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{26}N_2$ 246.2096 [M]$^+$, found 246.2105.

General Procedure for Synthesis of 3,5-Disubstituted Pyrazoles from Unsymmetric 1,3-Dialkynes. A reaction flask was charged with a mixture of unsymmetric 1,3-dialkynes (**3**, 0.4 mmol), aqueous hydrazine solution (50 wt %, 3.0 equiv, 76.9 mg), and DMSO (3.0 mL). The reaction mixture was sealed and stirred at 60 °C for 20 h and then was cooled to room temperature. Water (10 mL) was added to the resultant mixture. The product was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were washed with brine (10 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 20:1) to afford 3,5-disubstituted pyrazoles **4** and **5**.

5-Benzyl-3-(4-methoxyphenyl)-1*H*-pyrazole (4a). Yield: 41%, 43.3 mg, white solid, mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.29−7.20 (m, 5H), 6.84 (d, J = 8.0 Hz, 2H), 6.23 (s, 1H), 3.96 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 148.8, 147.9, 138.9, 128.9, 128.8, 127.1, 126.7, 124.8, 114.2, 101.6, 55.4, 33.4; IR (KBr) 3186, 2926,1615, 1509, 1495, 1250, 1030, 835, 719 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{16}N_2O$ 264.1263 [M]$^+$, found 264.1260.

5-(4-Fluorobenzyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (4b). Yield: 72%, 81.3 mg, white solid, mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.2 (dd, J = 5.6, 8.0 Hz, 2H), 6.93 (dd, J = 8.8, 8.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.19 (s, 1H), 3.89 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (d, ^1J = 242.7 Hz), 159.6, 148.4, 148.2, 134.6, 130.3 (d, ^3J = 7.8 Hz), 127.1, 124.4, 115.5 (d, ^2J = 21.2 Hz), 114.3, 101.5, 55.4, 32.6; IR (KBr) 3189, 3133, 3084, 3006, 2933, 2836, 1890, 1614, 1529, 1508, 1455, 1251, 1222, 1031, 835 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{15}N_2OF$ 282.1168 [M]$^+$, found 282.1168.

3-Hexyl-5-(4-methylbenzyl)-1*H*-pyrazole (4c). Yield: 61%, 62.6 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 5.79 (s, 1H), 3.90 (s, 2H), 2.55 (t, J = 8.0 Hz, 2H), 2.30 (s, 3H), 1.61−1.54 (m, 2H), 1.32−1.26 (m, 6H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.6, 136.5, 135,9, 129.3, 128.8, 102.8, 33.5, 31.8, 29.5, 29.2, 27.0, 22.7, 21.2, 14.3; IR (neat) 3190, 3132, 3100, 3021, 2927, 2857, 1900, 1578, 1514, 1495, 1433, 1023, 1005, 790 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}N_2$ 256.1939 [M]$^+$, found 256.1939.

3-Cyclohexyl-5-(4-methylbenzyl)-1*H*-pyrazole (4d). Yield: 64%, 65.1 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.78 (s, 1H), 3.91 (s, 2H), 2.61−2.55 (m, 1H), 2.31 (s, 3H), 1.95−1.66 (m, 5H), 1.40−1.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 149.1, 136.6, 135.9, 129.3, 128.9, 101.1, 36.3, 33.7, 33.1, 26.4, 26.2, 21.2; IR (neat) 3186, 3097, 3019, 2926, 2852, 1901, 1575, 1514, 1448, 1007, 987, 809 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}N_2$ 254.1783 [M]$^+$, found 254.1778.

3-(4-Methoxyphenyl)-5-(4-nitrobenzyl)-1*H*-pyrazole (4e). Yield: 87%, 107.6 mg, pale yellow solid, mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.20 (s, 1H), 3.97 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 148.2, 147.1, 146.9, 146.7, 129.5, 127.0, 123.8, 123.3, 114.3, 101.7, 55.4, 33.7; IR (KBr) 3134, 3012, 2934, 2837, 1606, 1572, 1513, 1346, 1251, 1029, 835, 729 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{15}N_3O_3$ 309.1113 [M]$^+$, found 309.1107.

5-(4-Nitrobenzyl)-3-phenyl-1*H*-pyrazole (4f). Yield: 90%, 100.5 mg, pale yellow solid, mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 6.4 Hz, 2H), 7.37−7.30 (m, 5H), 6.31 (s, 1H), 4.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.7, 130.7, 129.6, 129.1, 128.6, 125.7, 123.9, 102.5, 33.7; IR (KBr) 3104, 3011, 2930, 1604, 1516, 1345, 1013, 856, 729 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{13}N_3O_2$ 279.1008 [M]$^+$, found 279.1007.

3-Hexyl-5-(4-nitrobenzyl)-1*H*-pyrazole (4g). Yield: 89%, 102.3 mg, white solid, mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 5.80 (s,

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1H), 4.01 (s, 2H), 2.54 (t, J = 8.0 Hz, 2H), 1.59−1.51 (m, 2H), 1.30−1.23 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 147.6, 147.2, 146.6, 129.6, 123.8, 103.0, 34.2, 31.6, 29.2, 29.0, 26.3, 22.6, 14.1; IR (KBr) 3192, 3104, 2929, 2857, 1927, 1605, 1578, 1519, 1346, 857, 732 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{21}N_3O_2$ 287.1634 [M]$^+$, found 287.1640.

3-Cyclohexyl-5-(4-nitrobenzyl)-1*H*-pyrazole (4h). Yield: 94%, 107.3 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 5.79 (s, 1H), 4.01 (s, 2H), 2.58−2.53 (m, 1H), 1.91−1.64 (m, 5H), 1.37−1.13 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.6, 147.6, 146.6, 129.6, 123.7, 101.3, 35.8, 34.3, 32.9, 26.1, 25.9; IR (neat) 3190, 3103, 2928, 2852, 1923, 1599, 1573, 1518, 1346, 858, 729 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}N_3O_2$ 285.1477 [M]$^+$, found 285.1475.

5-Benzyl-3-hexyl-1*H*-pyrazole (4i). Yield: 78%, 75.6 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.29−7.20 (m, 5H), 5.82 (s, 1H), 3.97 (s, 2H), 2.58 (t, J = 8.0 Hz, 2H), 1.64−1.56 (m, 2H), 1.36−1.28 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.5, 139.6, 128.9, 128.7, 126.5, 102.9, 34.0, 31.8, 29.5, 29.2, 26.9, 22.7, 14.3; IR (neat) 3189, 3102, 3027, 2954, 2928, 2857, 1726, 1603, 1578, 1495, 1466, 1454, 722 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}N_2$ 242.1783 [M]$^+$, found 242.1791.

5-Benzyl-3-cyclohexyl-1*H*-pyrazole (4j). Yield: 81%, 77.9 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.28−7.17 (m, 5H), 5.78 (s, 1H), 3.94 (s, 2H), 2.60−2.54 (m, 1H), 1.94−1.65 (m, 5H), 1.40−1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 149.1, 139.8, 129.1, 128.8, 126.5, 101.3, 36.4, 34.3, 33.2, 26.5, 26.3; IR (neat) 3185, 3100, 3025, 2926, 2851, 1603, 1576, 1494, 1449, 1029, 1008, 718 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}N_2$ 240.1626 [M]$^+$, found 240.1630.

5-(4-Methoxybenzyl)-3-phenyl-1*H*-pyrazole (5a). Yield: 32%, 33.8 mg, white solid, mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.2 Hz, 2H), 7.31−7.20 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.26 (s, 1H), 3.88 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 147.8, 132.2, 130.5, 129.9, 128.9, 128.1, 125.7, 114.2, 102.0, 55.4, 32.4; IR (KBr) 3189, 2927, 1610, 1511, 1463, 1246, 1033, 766 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{16}N_2O$ 264.1263 [M]$^+$, found 264.1260.

3-(4-Fluorophenyl)-5-(4-methoxybenzyl)-1*H*-pyrazole (5b). Yield: 9%, 10.2 mg, white solid, mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.8, 5.2 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.99 (dd, J = 8.8, 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.24 (s, 1H), 3.87 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, ^1J = 245.2 Hz), 158.5, 149.3, 147.2, 130.3, 129.8, 128.8, 127.5 (d, ^3J = 8.0 Hz), 115.7 (d, ^2J = 21.5 Hz), 114.2, 101.8, 55.4, 32.0; IR (KBr) 3182, 3133, 3077, 3007, 2912, 2836, 1889, 1611, 1583, 1511, 1454, 1246, 839 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{15}N_2OF$ 282.1168 [M]$^+$, found 282.1170.

5-Heptyl-3-(*p*-tolyl)-1*H*-pyrazole (5c). Yield: 12%, 12.3 mg, white solid, mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.33 (s, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.37 (s, 3H), 1.71−1.64 (m, 2H), 1.39−1.25 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.3, 137.8, 129.8, 129.6, 125.6, 101.0, 31.9, 29.4, 29.2, 26.7, 21.4, 14.3; IR (KBr) 2950, 2926, 2850, 1900, 1580, 1566, 1464, 1425, 1041, 1017, 960, 821, 792 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}N_2$ 256.1939 [M]$^+$, found 256.1939.

5-(Cyclohexylmethyl)-3-(*p*-tolyl)-1*H*-pyrazole (5d). Yield: 12%, 12.2 mg, white solid, mp 45−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.31 (s, 1H), 2.51 (d, J = 6.8 Hz, 2H), 2.37 (s, 3H), 1.73−1.53 (m, 6H), 1.26−0.88 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 146.7, 137.7, 130.0, 129.5, 125.7, 101.7, 38.4, 34.5, 33.2, 26.5, 26.3, 21.4; IR (KBr) 3187, 3135, 3093, 2922, 2851, 1900, 1583, 1531, 1511, 1448, 1028, 822 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}N_2$ 254.1783 [M]$^+$, found 254.1778.

General Procedure for One-Pot Synthesis of 3,5-Disubstituted Pyrazoles from Alkynes. A reaction flask was charged with a mixture of terminal alkynes (**6**, 0.6 mmol), CuCl (3.0 mg, 5 mol %), and DMSO (3.0 mL). The reaction mixture was stirred at 90 °C for 8 h under air atmosphere and then was cooled to room temperature. Aqueous hydrazine solution (50 wt %, 1.5 equiv, 57.7 mg) was added to the resultant mixture, and then the mixture was sealed and stirred at 60 °C for 20 h. Water (10 mL) was added to the resultant mixture at room temperature. The product was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were washed with brine (10 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 3:1) to afford 3,5-disubstituted pyrazoles **2**.

5-(4-Butylbenzyl)-3-(4-butylphenyl)-1*H*-pyrazole (2i). Yield: 78%, 81.1 mg, white solid, mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.13−7.06 (m, 6H), 6.30 (s, 1H), 3.90 (s, 2H), 2.60−2.54 (m, 4H), 1.61−1.52 (m, 4H), 1.38−1.29 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 141.2, 136.0, 129.5, 128.9, 128.7, 125.7, 35.5, 35.4, 33.8, 33.7, 32.9, 22.54, 22.49, 14.1; IR (KBr) 2956, 2925, 2856, 1903, 1583, 1566, 1511, 1453, 963, 834 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{30}N_2$ 346.2409 [M]$^+$, found 346.2418.

5-(2-Methylbenzyl)-3-(*o*-tolyl)-1*H*-pyrazole (2j). Yield: 65%, 51.2 mg, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.6 Hz, 1H), 7.23−7.15 (m, 7H), 6.11 (s, 1H), 3.95 (s, 2H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 136.6, 136.1, 131.5, 130.9, 130.5, 129.6, 129.1, 128.2, 126.9, 126.3, 126.0, 105.0, 31.4, 21.0, 19.7; IR (neat) 3184, 3103, 3016, 2953, 2923, 1605, 1570, 1492, 1463, 762, 737 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}N_2$ 262.1470 [M]$^+$, found 262.1481.

5-(4-Bromobenzyl)-3-(4-bromophenyl)-1*H*-pyrazole (2k). Yield: 86%, 101.2 mg, white solid, mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.29 (s, 1H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 132.2, 132.1, 131.1, 130.7, 129.1, 129.0, 127.4, 122.3, 121.0, 102.6, 32.7; IR (KBr) 3126, 3101, 3004, 2920, 2854, 1894, 1636, 1487, 1072, 1007, 826, 802 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}N_2Br_2$ 389.9367, 391.9347 [M]$^+$, found 389.9375, 391.9350.

5-(4-Fluorobenzyl)-3-(4-fluorophenyl)-1*H*-pyrazole (2l). Yield: 88%, 71.4 mg, white solid, mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.59 (dd, J = 8.0, 5.6 Hz, 2H), 7.12 (dd, J = 8.0, 5.6 Hz, 2H), 7.00 (dd, J = 8.4, 8.4 Hz, 2H), 6.95 (dd, J = 8.4, 8.4 Hz, 2H), 6.25 (s, 1H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, ^1J = 245.7 Hz), 161.9 (d, ^1J = 243.5 Hz), 148.9, 147.2, 134.1, 130.2 (d, ^3J = 7.9 Hz), 128.4, 127.5 (d, ^3J = 8.1 Hz), 115.8 (d, ^2J = 20.8 Hz), 115.6 (d, ^2J = 20.5 Hz), 102.1, 32.3; IR (KBr) 3259, 1604, 1525, 1508, 1448, 1432, 1220, 841, 793 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}N_2F_2$ 270.0969 [M]$^+$, found 270.0970.

5-(3,4-Difluorobenzyl)-3-(3,4-difluorophenyl)-1*H*-pyrazole (2m). Yield: 86%, 79.0 mg, white solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.49−7.26 (m, 2H), 7.17−6.89 (m, 4H), 6.29 (s, 1H), 3.94 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.8 (dd, $^{1,2}J$ = 246.5, 12.6 Hz), 150.4 (dd, $^{1,2}J$ = 247.8, 12.9 Hz), 149.5 (dd, $^{1,2}J$ = 246.0, 12.3 Hz), 149.3, 135.0, 129.4, 124.6 (d, ^3J = 3.4 Hz), 121.9 (d, ^3J = 3.3 Hz), 117.8 (d, ^2J = 17.8 Hz), 117.66, 117.61 (d, ^2J = 17.8 Hz), 114.8 (d, ^2J = 18.3 Hz), 102.6, 32.1; IR (KBr) 3176, 1610, 1530, 1518, 1478, 1281, 773 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{10}N_2F_4$ 306.0780 [M]$^+$, found 306.0782.

3-(Naphthalen-1-yl)-5-(naphthalen-1-ylmethyl)-1*H*-pyrazole (2n). Yield: 60%, 60.2 mg, pale yellow solid, mp 84− 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.80−7.64 (m, 4H), 7.44−7.18 (m, 8H), 6.18 (s, 1H), 4.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 134.8, 134.0, 133.9, 132.0, 131.4, 130.0, 128.8, 128.7, 128.4, 127.5, 127.2, 126.9, 126.5, 126.2, 126.0, 125.82, 125.75, 125.7, 125.3, 124.1, 30.7; IR (KBr) 2970, 1633, 1597, 1509, 1397, 777 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{18}N_2$ 334.1470 [M]$^+$, found 334.1464.

3-((3-(Pyridin-3-yl)-1*H*-pyrazol-5-yl)methyl)pyridine (2o). Yield: 80%, 56.7 mg, white solid, mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.95 (d, J = 1.6 Hz, 1H), 8.50−8.43 (m, 3H), 8.02−7.99 (m, 1H),7.54 (d, J = 8.0 Hz, 1H), 7.29−7.18 (m, 2H), 6.40 (s, 1H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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149.5, 148.6, 147.8, 146.8, 136.5, 134.3, 133.0, 128.5, 123.73, 123.72, 102.4, 30.1; IR (KBr) 3195, 3113, 3084, 2844, 1727, 1577, 1444, 1435, 1422, 1029, 810, 704 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{12}N_4$ 236.1062 $[M]^+$, found 236.1057.

3-(Thiophen-3-yl)-5-(thiophen-3-ylmethyl)-1H-pyrazole (2p). Yield: 78%, 57.6 mg, white solid, mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.34−7.23 (m, 3H), 6.96−6.91 (m, 2H), 6.24 (s, 1H), 3.94 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 145.0, 138.8, 133.5, 128.4, 126.3, 126.0, 121.8, 121.0, 102.2, 27.8; IR (KBr) 3204, 3136, 3093, 2889, 1600, 1474, 1431, 1010, 854, 784, 737 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{10}N_2S_2$ 246.0285 $[M]^+$, found 246.0283.

■ ASSOCIATED CONTENT

Supporting Information

Characterization for compounds, including copies of ^1H and ^{13}C NMR spectra and crystallographic data of **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yuxiaoqiang@dlut.edu.cn; mingbao@dlut.edu.cn.

Notes

The authors declare no competing financial interest.

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