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Regioselective rapid analog synthesis of 1,3-(or 1,5-)diphenyl-4-aryl/heteroaryl-5-(or 3-)(methylthio)pyrazoles via Suzuki cross-coupling

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ABSTRACT

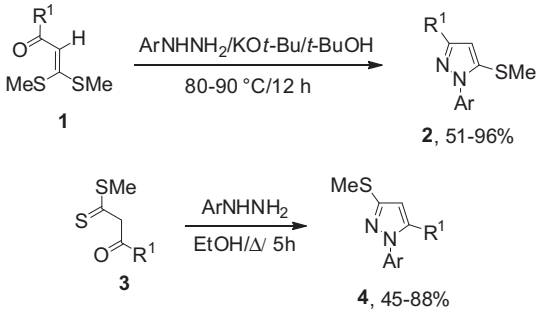
Regioselective routes for the synthesis of 1,3-(or 1,5-)diphenyl-4-aryl/heteroaryl-5-(or 3-)(methylthio)-pyrazoles via Suzuki cross-coupling of 4-bromo (or 4-iodo)-1,3-(or 1,5-)diphenyl-5-(or 3-)(methylthio)-pyrazoles have been reported.

1. Introduction

Substituted pyrazoles, though rarely found in nature, serve as important targets in medicinal chemistry and pharmaceutical industry because the pyrazole motif constitutes the core structure of numerous biologically active compounds[1] including block buster drugs, such as celebrex,[2] viagra,[3] and acomplia. Numerous 1,3,5- and 1,3,4,5-substitued pyrazoles are being developed in a wide range of therapeutical areas including anti-inflammatory,[4] anticancer,[5] antibacterial,[6] analgesic,[7] CNS-,[8] endothelin-antagonists[9] as well as in agrochemistry to obtain herbicides[10] and pesticides.[11] As a result, there is continuing interest in the development of versatile methods to access highly substituted pyrazoles.[12]

While there are many novel methods available for the assembly of substituted pyrazoles, perhaps the most commonly used and convenient method remains the condensation of 1,3-dicarbonyl compounds or their equivalents with a hydrazine derivative (Knorr reaction).[1] However, this route often suffers major drawback of poor regioselectivity during ring annulation yielding inseparable mixture of isomeric pyrazoles.[13] Another important method involving 1,3-dipolar cycloaddition of diazoalkanes or nitrileimines with olefins and alkynes has found only limited application because 1,3-dipoles are often difficult to prepare and potentially explosive.[14] Although recent efforts have greatly expanded the generality of these de novo approaches, each method has its scope and efficiency limitations.[14b,15] Since subtle variation and combination of arylation pattern on the pyrazole motif has profound effect on the biological activity,[2,5b,16] efficient and simple protocols by which the pyrazole ring could be elaborated in a regiocontrolled fashion to polysubstituted pyrazoles at a later stage of the reaction sequence are highly desirable.

We have recently reported an efficient general regiocontrolled synthesis of 1-aryl-3,4- or 4,5-substitued 5-(or 3-)(methylthio)pyrazoles by cyclocondensation of aryl hydrazines with either α-oxoketene dithioacetals or β-oxodithioesters, respectively (Scheme 1).[17]



1-4, R^1 = substituted aryl, alkyl, 3-pyridyl, $CH(OMe)_2$
2, **4**, Ar = C_6H_5, 4-FC_6H_4

Scheme 1.

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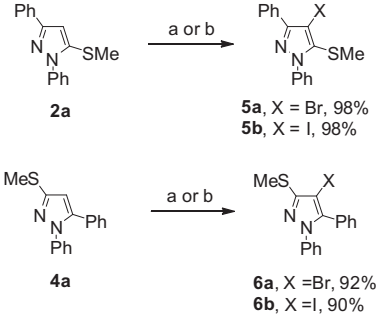
The 5-(or 3)(methylthio) functionality in these isomeric pyrazoles could be further elaborated for regioselective introduction of 5-(or 3-) aryl/alkyl groups by nickel-catalyzed cross-coupling with the appropriate Grignard reagents. The methodology was also applied for the regioselective synthesis of 4-ethyl-1,3,5-triarylpyrazoles as estrogen receptor ligands.[17] With a number of isomeric 1,3-(or 1,5-) diaryl-5-(or 3-)(methylthio)pyrazoles in hand from readily accessible precursors, we further envisaged of introducing more diversity in these trisubstituted pyrazoles by installing a 4-aryl/heteroaryl moiety thus leading to the regiospecific synthesis of isomeric tetrasubstituted pyrazoles. We choose to investigate transition metal catalysis for introduction of a 4-aryl/heteroaryl group into these fully assembled trisubstituted pyrazoles. Of particular interest was Suzuki cross-coupling reaction,[18] as it is well established dependable process, widely used in pharmaceutical industry[19] utilizing commercially available boronic acids as the organometallic coupling partners. This reaction is also unaffected by the presence of water and is compatible with broad range of functional groups on both partners. Our literature survey revealed that there have been few reports of Suzuki cross-coupling reactions performed on *N*-aryl/alkyl mono and disubstituted halopyrazoles.[20,21] Also, there have been few reports of Suzuki cross-coupling accomplished with pyrazole triflates,[22] nonaflates[23] as well as pyrazole boronic acid derivatves.[24,25]

In the present paper, we wish to highlight the results of our investigation on synthetic elaboration of regioisomeric 1,3-diphenyl-5-(methylthio) and 1,5-diphenyl-3-(methylthio)pyrazoles to novel unsymmetrically tetrasubstituted 5- or 3-(methylthio)pyrazoles via Suzuki cross-coupling in highly regiocontrolled fashion. Reductive dethiomethylation of few of these newly synthesized (methylthio) pyrazoles to the corresponding 1,3,4- or 1,4,5-triaryl/heteroaryl pyrazoles with Raney nickel is also described.

2. Results and discussion

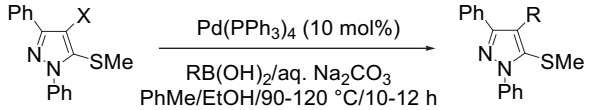
The isomeric 1,3-diphenyl-5-(methylthio) and 1,5-diphenyl-3-(methylthio)pyrazoles **2a** and **4a** were selected as the corresponding partners for their further elaboration at 4-position by Suzuki coupling with various boronic acids (Scheme 2). The pyrazoles **2a** (R^1=Ph) and **4a** (R^1=Ph) were prepared by our earlier reported[17] procedure from the corresponding α-oxoketene dithioacetal **1** (R^1=Ph) or β-oxodithioester **3** (R^1=Ph) by treatment with phenyl hydrazine under different reaction conditions as outlined in the Scheme 1. The desired 4-halopyrazole cross-coupling templates (**5** and **6**) were generated from **2a** and **4a** by treatment with either NBS or iodine mono chloride furnishing the isomeric 4-bromo (or 4-iodo) 1,3- (or 1,5-)diphenyl-5-(or 3-)(methylthio)pyrazoles **5a**,**b** and **6a**,**b** in excellent yields (Scheme 2).

Pyrazoles **5a**,**b** were chosen to define optimal reaction conditions for their 4-arylation with phenyl boronic acid **11a** under standard Suzuki cross-coupling reaction conditions. Initial studies involved using $PdCl_2(PPh_3)_2$ as Pd(0) catalyst in the presence of Na_2CO_3 as base in DME/H_2O solvent, which gave **7a** (from **5a**) in modest yield (52%). However, efficient cross-coupling (with **5a**) could be accomplished by switching over to $Pd(PPh_3)_4$ (10 mol %) as palladium source, Na_2CO_3 (5 equiv) as base, and toluene/ethanol/water solvent under reflux, which afforded **7a** in 80% yield (Table 1,



Scheme 2.

Table 1
Synthesis of 4-aryl/heteroaryl-5-(methylthio)-1,3-diphenylpyrazoles **7**



5a-b **7a-j**

Entry	5	Boronic acid	7	Yield 7 (%)
1	**5a**	**11a**, X=H	**7a**, X=H	80 (83)[a]
2	**5b**	**11b**, X=OMe	**7b**, X=OMe	75
3	**5b**	**11c**, X=MeCO	**7c**, X=MeCO	51
4	**5a**	**11d**, X=S	**7d**, X=S	50
5	**5a**	**11e**, X=O	**7e**, X=O	30 (70)[b]
6	**5b**	**11f**	**7f**	0 (0)[b]
7	**5a**	**11g**	**7g**	60
8	**5a**	**11h**	**7h**	52
9	**5b**	**11i**	**7i**	68
10	**5b**	**11j**	**7j**	70

[a] Yield of **7a** with **5b**.
[b] Reaction condition: $Pd(OAc)_2$ (4 mol %)/*S*-Phos (10 mol %)/K_3PO_4 (2 equiv)/toluene/reflux/36 h.

entry 1).[26] These optimized reaction conditions were applied throughout our studies (with one exception) to further probe the scope of this cross-coupling reaction with various aryl/heteroaryl boronic acids and the results are demonstrated in Table 1. Thus these reactions were found to be compatible with electron rich (4-methoxyphenyl)boronic acid **11b** to give 4-(4-methoxyphenyl) pyrazole **7b** in 75% yield (entry 2). However, the coupling of the boronic acid **11c** bearing an electron withdrawing 4-acetyl functionality gave only modest yield (51%) of the 4-(4-acetylphenyl) pyrazole **7c** under identical conditions (Table 1, entry 3) and no attempts were made to further optimize the reaction conditions for improved yield of **7c**. Entries 4–10 demonstrate the scope of this coupling protocol with various heteroaryl boronic acids (Table 1). Thus, the reaction of the thiophene-2-boronic acid with **5a** under the above described conditions provided 4-(2-thienyl)pyrazole **7d** in 50% yield (entry 4, see Fig. 1 for X-ray diagram of **7d**[27]). However, these reaction conditions were not compatible for cross-coupling of 2-furyl and 3-pyridyl boronic acids **11e**,**f** with either **5a** or **5b** resulting in low yield (30%) of the pyrazole **7e** (entry 5), while no trace of the 4-(3-pyridyl)pyrazole **7f** could be isolated from the reaction mixture under these conditions furnishing only unreacted starting materials **11f** and **5b** (entry 6). Nevertheless, switching over to electron rich bulky ligand *S*-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl), $Pd(OAc)_2$ (4 mol %) as palladium source and K_3PO_4 (2 equiv) as base dramatically improved the yield of **7e** (70%) (entry 5), whereas the 4-(3-pyridyl)pyrazole **7f** could not also be obtained under these modified conditions even in low yield (entry 6).

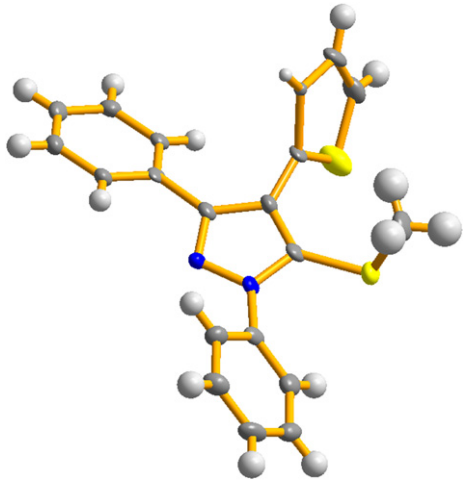
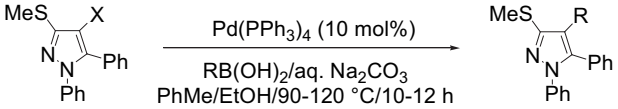


Fig. 1. ORTEP diagram of **7d**.

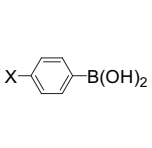
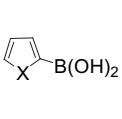
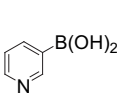
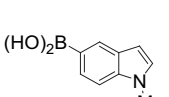
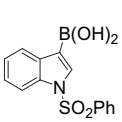
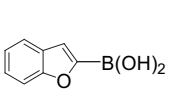
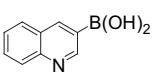
Additional structural diversity at the 4-position of the pyrazole **5a**,**b** could be introduced by their cross-coupling with boronic acids **11g**–**j** derived from benzoheterocycles (entries 7–10). Thus, both 5- and 3-indolyl boronic acids **11g**,**h** were well tolerated as coupling partners with **5a** under our optimized reaction conditions yielding 4-[5-(*N*-methyl)indolyl]- and 4-[3-(*N*-phenyl sulfonyl)indolyl]-pyrazoles **7g**,**h** in 60% and 52% yields, respectively (entries 7,8). Similarly, effective cross-coupling could also be accomplished with 2-(benzofuryl)- and 3-(quinolinyl)-boronic acids **11i**,**j** providing the corresponding 4-(2-benzofuryl) and 4-(3-quinolinyl)pyrazoles in good yields under similar reaction conditions (Table 1, entries 9,10).

We next extended our Suzuki cross-coupling protocol for the synthesis of regioisomeric 1,5-diphenyl-3-(methylthio)-4-aryl/heteroarylpyrazoles **8a**–**j** by utilizing 1,5-diphenyl-3-(methylthio)-4-bromo/iodopyrazoles **6a**,**b** as cross-coupling templates in their reaction with various aryl/heteroaryl boronic acids **11a**–**j**. These results are highlighted in Table 2. Thus, reasonably good yields of 4-aryl-1,5-diphenyl-3-(methylthio)pyrazoles **8a**–**c** were obtained when **6a** or **6b** were subjected to cross-coupling with aryl boronic acids **11a**–**c** under our earlier optimized conditions (Table 2, entries 1–3). Interestingly, the coupling reaction of **6b** also proceeded smoothly with 2-thienyl and 3-pyridyl boronic acids **11d** and **11f**

Table 2
Synthesis of 3-methylthio-4-aryl/heteroaryl-1,5-diphenylpyrazoles **8**



6a-b **8a-j**

Entry	**6**	Boronic acid	**8**	Yield **8** (%)
				
1	**6a**	**11a**, X=H	**8a**, X=H	78 (83)[a]
2	**6b**	**11b**, X=OMe	**8b**, X=OMe	84
3	**6b**	**11c**, X=MeCO	**8c**, X=MeCO	68
				
4	**6b**	**11d**, X=S	**8d**, X=S	62
5	**6a**	**11e**, X=O	**8e**, X=O	63[b]
				
6	**6b**	**11f**	**8f**	62
				
7	**6b**	**11g**	**8g**	72
				
8	**6a**	**11h**	**8h**	55
				
9	**6a**	**11i**	**8i**	75
				
10	**6b**	**11j**	**8j**	80

[a] Yield of **8a** with **6b**.
[b] Reaction condition: $Pd(OAc)_2$ (4 mol %)/*S*-Phos (10 mol %)/K_3PO_4 (2 equiv)/toluene/reflux/20 h.

under these optimized conditions (unlike with **5a**,**b**) affording the corresponding 3-(methylthio)-4-(2-thienyl) and 4-(3-pyridyl)pyrazoles **8d** and **8f** both in 62% yield (entries 4 and 6; see Fig. 2 for X-ray diagram of **8d**[27]). On the other hand, the reaction of **6a** with 2-furyl boronic acid **11e** under identical reaction conditions yielded only inseparable mixture of 4-(2-furyl)-3-(methylthio)pyrazole **8e** and **6a**, however, pure **8e** could be obtained in 63% yield under modified reaction conditions ($Pd(OAc)_2$/*S*-Phos/K_3PO_4) (Table 2, entry 5) earlier applied for the synthesis of isomeric **7e**. Similarly, benzo-fused heteroaryl boronic acids **11g**–**j** also participated readily in Suzuki cross-coupling reaction with pyrazoles **6a** or **6b** under above described conditions affording 1,5-diphenyl-3-(methylthio)-4-(2/3/5-heteroaryl) pyrazoles **8g**–**j** in satisfactory yields (Table 2, entries 7–10).[27]

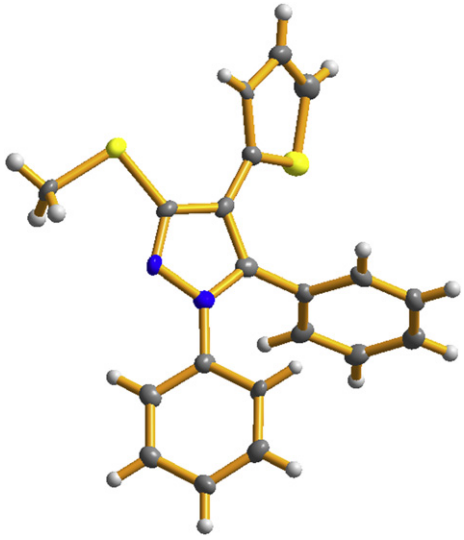
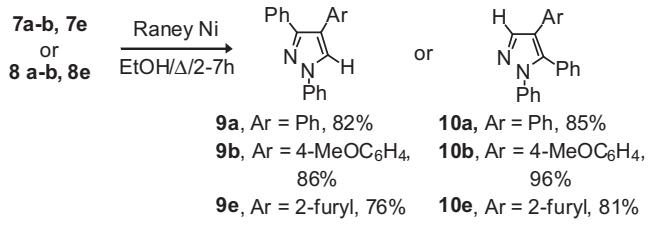


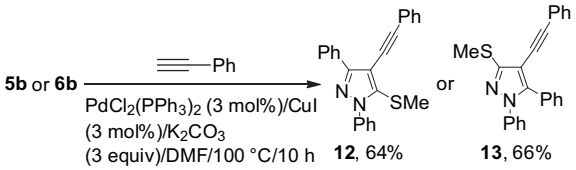
Fig. 2. ORTEP diagram of **8d**.

In order to complete our synthetic exploration, a few of these newly synthesized tetrasubstituted isomeric 5-(or 3-)(methylthio) pyrazoles **7** and **8** were subjected to reductive dethiomethylation in the presence of Raney-Ni since this would provide a regioselective route for the synthesis of unsymmetrical 1,3,4- and 1,4,5-trisubstituted pyrazoles (Scheme 3). Thus, the desulfurization of the pyrazoles **7a**,**b**,**e**, **8a**,**b** and **e** proceeded smoothly in the presence of Raney-Ni in refluxing ethanol yielding the isomeric 1,3-diphenyl-4-aryl/heteroaryl- (**9a**,**b**,**e**) and 1,5-diphenyl-4-aryl/heteroaryl (**10a**,**b**,**e**) pyrazoles in excellent yields (Scheme 3).



Scheme 3.

The regioisomeric 4-iodopyrazoles **5b** and **6b** also participated readily in Sonogashira coupling reaction with phenylacetylene under standard conditions to afford tetrasubstituted 1,3-(or 1,5-) diphenyl-5-(or 3-)(methylthio)-4-(phenylethynyl)pyrazoles **12** and **13** in good yields in highly regiocontrolled fashion (Scheme 4).



Scheme 4.

3. Conclusion

In summary, we have developed a general regioselective flexible route for hitherto unreported novel tetrasubstitued 3- and 5-(methylthio)-1,4,5-triaryl/heteroaryl and 1,3,4-triaryl/heteroarylpyrazoles. The synthesis relies on installing an aryl/heteroaryl group at the C-4 position of the 1,3,5-trisubstituted pyrazoles through halogenation followed by the Suzuki cross-coupling with a series of aryl/heteroaryl boronic acids. The coupling conditions were found to be tolerant for a broad range of aryl/heteroaryl boronic acid components. Also, this approach avoids necessity to 'custom make' difficultly accessible unsymmetrical desoxybenzoin precursors required for our previous approaches (conventional approaches),[17] involving cyclocondenastion of α-oxoketene dithioacetals with aryl hydrazines. Subsequent reductive dethiomethylation of these tetrasubstituted pyrazoles provides regioselective route for the synthesis[25] of unsymmetrical 1,3,4- and 1,4,5-triaryl pyrazoles. It should be noted that 1,3,4-trisubstituted pyrazoles, though pharmaceutically important,[4a,5b,28] yet are less represented in the literature, probably due to synthetic difficulties, since the Knorr condensation of the substituted hydrazines with β-keto aldehydes usually favors 1,4,5-trisubstituted pyrazoles.[28] The (methylthio) functionality in these isomeric 5- and 3-(methylthio) tetrasubstituted pyrazoles can be further elaborated[29] for introducing functional group diversity at 5- or 3-position by nickel-catalyzed cross-coupling with alkyl or aryl Grignard reagents as demonstrated in our earlier studies.[17] Our efforts in this direction are under progress.

4. Experimental section

4.1. General

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol JNM Lambda Spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1320 spectrometer. Mass spectra were recorded on Jeol SX 102/DA-6000 Mass Spectrometer/Data System. Elemental analyses were carried out on a Elementar Vario EL III analyzer at Central Drug Research Institute, Lucknow (India).

All boronic acids were obtained from commercial sources.

4.2. Procedure for the preparation of 4-bromo-5-(methylthio)-1,3-diphenyl- and 4-bromo-3-(methylthio)-1,5-diphenyl-1*H*-pyrazoles (5a, 6a)

Pyrazole **2a** or **4a** (0.50 g, 1.88 mmol) was dissolved in CCl_4 (20 mL) and NBS (0.30 g, 2.0 mmol) was added to the solution at room temperature. Reaction mixture was further stirred at room temperature for 1 h (monitored by TLC). It was then filtered on Buchner funnel and residue was washed with CCl_4 (3×5 mL). Filtrate was concentrated under reduced pressure to give bromopyrazoles, which were purified by column chromatography over silica gel using hexane/EtOAc (9:1) as eluent.

*4.2.1. 4-Bromo-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**5a**).* Yield 98% (0.63 g); light yellow solid; mp 80 °C; R_f 0.38 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3034, 2919, 1591, 1490, 1447, 1303, 963, 766,

691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H, SCH_3), 7.29 (t, J=7.0 Hz, 1H, ArH), 7.35 (t, J=7.8 Hz, 2H, ArH), 7.40 (t, J=8.0 Hz, 3H, ArH), 7.53 (dd, J=8.1, 1.4 Hz, 2H, ArH), 7.88 (dd, J=8.3, 1.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 102.4, 125.4, 127.6, 128.3, 128.4, 128.5, 128.8, 131.6, 136.1, 139.5, 149.5; MS (m/z, %): 347 (M^+, 100), 345 (M^+, 95). Anal. Calcd for $C_{16}H_{13}BrN_2S$ (345.26): C, 55.66; H, 3.80; N, 8.11%. Found C, 55.73; H, 3.77; N, 7.95%.

*4.2.2. 4-Bromo-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**6a**).* Yield 83% (0.54 g); light yellow solid; mp 78–79 °C; R_f 0.38 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3063, 2923, 1591, 1494, 1346, 1022, 963, 771, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, SCH_3), 7.17–7.18 (m, 1H, ArH), 7.19 (d, J=1.9 Hz, 1H, ArH), 7.21–7.28 (m, 5H, ArH), 7.33 (dd, J=5.0, 1.9 Hz, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 96.9, 124.5, 127.4, 128.4, 128.5, 128.8, 129.0, 129.8, 139.6, 141.7, 147.7; MS (m/z, %): 347 (M^+, 98), 345 (M^+, 100). Anal. Calcd for $C_{16}H_{13}BrN_2S$ (345.26): C, 55.66; H, 3.80; N, 8.11%. Found C, 55.54; H, 3.81; N, 8.10%.

4.3. Procedure for the preparation of 1,3-diphenyl-4-iodo-5-(methylthio) and 1,5-diphenyl-4-iodo-3-(methylthio) pyrazoles (5b, 6b)

To a mixture of pyrazole **2a** or **4a** (0.50 g, 1.88 mmol), CH_3COONa (0.17 g, 2.0 mmol), and acetic acid (3.0 mL), iodine mono chloride (0.10 mL, 2.0 mmol) was added at room temperature. Reaction mixture was further stirred at room temperature for 1 h (monitored by TLC). It was then poured into 30 mL of cold water and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with water (2×50 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give products, which were purified by column chromatography over silica gel using hexane/EtOAc (9:1) as eluent.

*4.3.1. 4-Iodo-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**5b**).* Yield 98% (0.72 g); light yellow solid; mp 131–132 °C; R_f 0.38 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3049, 2921, 1592, 1494, 1444, 960, 761, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H, SCH_3), 7.31 (t, J=7.3 Hz, 1H, ArH), 7.37 (t, J=7.3 Hz, 2H, ArH), 7.42 (t, J=7.8 Hz, 3H, ArH), 7.53 (dd, J=8.5, 1.4 Hz, 2H, ArH), 7.82 (dd, J=8.2, 1.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.96, 72.75, 125.55, 128.20, 128.24, 128.51, 128.53, 128.82, 132.46, 139.78, 153.02; MS (m/z, %): 393 (M^++1, 100), 392 (M^+, 30). Anal. Calcd for $C_{16}H_{13}IN_2S$ (392.26): C, 48.99; H, 3.34; N, 7.14%. Found C, 48.81; H, 3.46; N, 7.19%.

*4.3.2. 4-Iodo-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**6b**).* Yield 88% (0.65 g); light yellow solid; mp 106–107 °C; R_f 0.38 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3047, 2921, 1592, 1493, 1445, 961, 770, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H, SCH_3), 7.09–7.10 (m, 1H, ArH), 7.11 (d, J=7.3 Hz, 1H, ArH), 7.13–7.20 (m, 5H, ArH), 7.27 (dd, J=5.0, 1.9 Hz, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 65.7, 124.4, 127.3, 128.4, 128.7, 128.9, 129.5, 130.0, 139.6, 144.9, 151.2; MS (m/z, %): 393 (M^++1, 100), 392 (M^+, 25). Anal. Calcd for $C_{16}H_{13}IN_2S$ (392.26): C, 48.99; H, 3.34; N, 7.14%. Found C, 49.26; H, 3.17; N, 7.26%.

4.4. General procedure for Suzuki cross-coupling of aryl/heteroaryl boronic acids with 1,3-(or 1,5)-diphenyl-4-halo-5-(or 3-)(methylthio)pyrazoles 5a,b and 6a,b: synthesis of 1,3-(or 1,5-)diphenyl-4-aryl/heteroaryl-5-(or 3-)(methylthio) pyrazoles 7a–j and 8a–j

In a typical experiment, a mixture of 4-halopyrazole **5a**,**b** or **6a**,**b** (1.27 mmol), aryl/heteroaryl boronic acids **11a**–**j** (1.90 mmol), Pd(PPh_3)$_4$ (146 mg, 0.127 mmol), EtOH (3.0 mL), and 2 M solution of aq Na_2CO_3 (3.0 mL) in toluene (8.0 mL) was heated at 90–120 °C for 10–12 h (monitored by TLC). The reaction mixture was then poured into 30 mL of cold water and extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with water (2×50 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give products, which were purified by column chromatography over silica gel using hexane/EtOAc as eluent (7.5:2.5).

*4.4.1. 5-(Methylthio)-1,3,4-triphenyl-1H-pyrazole (**7a**)[17].* Yield 80% (0.34 g); colorless solid; mp 97–98 °C; R_f 0.47 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3058, 2921, 1678, 1594, 1494, 1436, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H, SCH_3), 7.17–7.19 (m, 3H, ArH), 7.31–7.32 (m, 5H, ArH), 7.36 (t, J=7.3 Hz, 1H, ArH), 7.42–7.46 (m, 4H, ArH), 7.66 (d, J=7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 125.7, 125.8, 127.3, 127.7, 128.06, 128.08, 128.2, 128.3, 128.8, 130.4, 132.8, 132.9, 134.4, 139.7, 150.0.

*4.4.2. 4-(4-Methoxyphenyl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7b**).* Yield 75% (0.35 g); colorless solid; mp 115–116 °C; R_f 0.31 (9.0:1.0 hexanes/EtOAc); IR (KBr): 3005, 2932, 2833, 1594, 1537, 1490, 1438, 1245, 1031, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 6.85 (d, J=8.5 Hz, 2H, ArH), 7.18 (dd, J=5.1, 1.9 Hz, 3H, ArH), 7.21 (d, J=8.5 Hz, 2H, ArH), 7.33 (t, J=7.3 Hz, 1H, ArH), 7.40–7.44 (m, 4H, ArH), 7.64 (d, J=7.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 55.1, 124.9, 125.3, 125.6, 127.6, 128.0, 128.04, 128.1, 128.8, 131.4, 132.7, 134.2, 139.6, 149.9, 158.7; MS (m/z, %): 373 (M^++1, 100), 372 (M^+, 92). Anal. Calcd for $C_{23}H_{20}N_2OS$ (372.48): C, 74.16; H, 5.41; N, 7.52%. Found C, 73.96; H, 5.24; N, 7.33%.

*4.4.3. 4-(4-Acetylphenyl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7c**).* Yield 51% (0.25 g); white solid; mp 145–146 °C; R_f 0.32 (9.0:1.0 hexanes/EtOAc); IR (KBr): 3056, 2920, 1679, 1601, 1496, 1261, 964, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.89 (s, 3H, SCH_3), 2.58 (s, 3H, $COCH_3$), 7.22–7.24 (m, 3H, ArH), 7.40 (d, J=7.08 Hz, 3H, ArH), 7.46 (t, J=8.2 Hz, 4H, ArH), 7.68 (d, J=7.8 Hz, 2H, ArH), 7.93 (d, J=8.32 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 26.6, 124.5, 125.7, 128.0, 128.2, 128.31, 128.35, 128.9, 130.5, 132.3, 134.6, 135.7, 137.9, 139.4, 150.2, 197.8; MS (m/z, %): 385 (M^++1, 100), 384 (M^+, 37). Anal. Calcd for $C_{24}H_{20}N_2OS$ (384.49): C, 74.97; H, 5.24; N, 7.29%. Found C, 74.85; H, 5.17; N, 7.50%.

*4.4.4. 5-(Methylthio)-1,3-diphenyl-4-(thiophen-2-yl)-1H-pyrazole (**7d**).* Yield 50% (0.22 g); white solid; mp 107–108 °C; R_f 0.4 (9:1 hexanes/EtOAc); IR (KBr): 3061, 2922, 1592, 1493, 1443, 1376, 1077, 758, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, SCH_3), 7.02 (d, J=2.6 Hz, 1H, ArH), 7.06 (t, J=4.8 Hz, 1H, ArH), 7.31 (dd, J=4.8, 1.7 Hz, 3H, ArH), 7.37 (d, J=4.8 Hz, 1H, ArH), 7.43 (t, J=7.3 Hz, 1H, ArH), 7.51 (t, J=7.8 Hz, 2H, ArH), 7.56–7.58 (m, 2H, ArH), 7.69 (d, J=7.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 118.9, 125.7, 126.1, 127.1, 127.9, 128.0, 128.23, 128.26, 128.8, 132.5, 133.5, 135.3, 139.5, 150.7; MS (m/z, %): 349 (M^++1, 100), 348 (M^+, 72). Anal. Calcd for $C_{20}H_{16}N_2S_2$ (348.49): C, 68.93; H, 4.63; N, 8.04%. Found C, 68.84; H, 4.72; N, 8.10%.

*4.4.5. 4-(Furan-2-yl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7e**).* Yield 30% (0.13 g); yellow solid; mp 85–86 °C; R_f 0.41 (9:1 hexanes/EtOAc); IR (KBr): 3053, 2925, 1592, 1493, 1075, 764, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H, SCH_3), 6.41–6.44 (m, 2H, Ar), 7.25 (d, J=7.3 Hz, 3H, ArH), 7.35 (t, J=7.3 Hz, 1H, ArH), 7.40–7.44 (m, 3H, ArH), 7.49 (dd, J=7.8, 1.9 Hz, 2H, ArH), 7.59 (dd, J=7.9, 1.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 109.8, 111.1, 115.7, 125.7, 127.8, 128.0, 128.2, 128.3, 128.8, 132.6, 135.8, 139.4, 142.2, 146.2, 150.7; MS (m/z, %): 333 (M^++1, 100), 332 (M^+, 78). Anal. Calcd for $C_{20}H_{16}N_2OS$ (332.42): C, 72.26; H, 4.85; N, 8.43%. Found C, 72.47; H, 4.75; N, 8.32%.

*4.4.6. 4-(1-Methyl-lH-indol-5-yl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7g**).* Yield 60% (0.30 g); white solid; mp 168–170 °C; R_f 0.44 (7.5:2.5 hexane/EtOAc); IR (KBr): 3060, 2923, 1593, 1496, 1443,

1370, 1328, 1078, 759, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H, SCH_3), 3.82 (s, 3H, NCH_3), 6.51 (d, J=2.9 Hz, 1H, ArH), 7.08 (d, J=2.9 Hz, 1H, ArH), 7.20–7.25 (m, 4H, ArH), 7.35 (d, J=7.8 Hz, 1H, ArH), 7.44 (d, J=7.3 Hz, 1H, ArH), 7.51–7.57 (m, 4H, ArH), 7.68 (dd, J=5.2, 1.4 Hz, 1H, ArH), 7.78 (d, J=7.3 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 32.8, 101.1, 109.1, 122.7, 123.7, 124.2, 124.6, 125.6, 127.5, 127.9, 128.0, 128.2, 128.4, 128.7, 129.1, 132.9, 136.0, 139.7, 149.9; MS (m/z, %): 396 (M^++1, 100), 395 (M^+, 95). Anal. Calcd for $C_{25}H_{21}N_3S$ (395.52): C, 75.92; H, 5.35; N, 10.62%. Found C, 76.06; H, 5.35; N, 10.73%.

*4.4.7. 4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7h**).* Yield 52% (0.34 g); white solid; mp 82–83 °C; R_f 0.32 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3058, 2923, 1596, 1497, 1444, 1373, 1178, 750, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 3H, SCH_3), 7.02 (t, J=7.3 Hz, 3H, ArH), 7.10 (t, J=7.0 Hz, 2H, ArH), 7.23 (t, J=7.3 Hz, 1H, ArH), 7.33–7.38 (m, 5H, ArH), 7.45 (t, J=8.4 Hz, 3H, ArH), 7.57 (s, 1H, ArH), 7.66 (d, J=7.5 Hz, 2H, ArH), 7.80 (dd, J=8.2, 1.2 Hz, 2H, ArH), 7.98 (d, J=8.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 113.8, 115.5, 115.9, 121.0, 123.4, 124.9, 125.5, 125.7, 126.7, 127.3, 127.8, 128.20, 128.23, 128.8, 129.2, 130.4, 132.5, 133.7, 135.2, 136.0, 138.1, 139.5, 158.8; MS (m/z, %): 521 (M^+, 47). Anal. Calcd for $C_{30}H_{23}N_3O_2S_2$ (521.65): C, 69.07; H, 4.44; N, 8.06%. Found C, 68.84; H, 4.31; N, 8.01%.

*4.4.8. 4-(Benzofuran-2-yl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7i**).* Yield 68% (0.33 g); white solid; mp 152–154 °C; R_f 0.40 (9:1 hexanes/EtOAc); IR (KBr): 3057, 2921, 1592, 1496, 1449, 1250, 972, 776, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.99 (s, 3H, SCH_3), 7.80 (s, 1H, ArH), 8.14–8.22 (m, 5H, ArH), 8.36 (d, J=7.0 Hz, 2H, ArH), 8.42 (t, J=7.0 Hz, 2H, ArH), 8.49–8.52 (m, 3H, ArH), 8.60 (d, J=7.3 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 106.3, 111.2, 115.3, 120.8, 122.7, 124.0, 125.8, 128.0, 128.2, 128.4, 128.8, 128.9, 132.4, 136.5, 139.3, 148.3, 151.0, 154.7; MS (m/z, %): 383 (M^++1, 100), 382 (M^+, 90). Anal. Calcd for $C_{24}H_{18}N_2OS$ (382.48): C, 75.37; H, 4.74; N, 7.32%. Found C, 75.43; H, 4.90; N, 7.30%.

*4.4.9. 4-(Quinolin-3-yl)-5-(methylthio)-1,3-diphenyl-1H-pyrazole (**7j**).* Yield 70% (0.35 g); white solid; mp 156–157 °C; R_f 0.31 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3056, 2919, 1595, 1493, 1448, 1340, 762, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.86 (s, 3H, SCH_3), 7.17–7.20 (m, 3H, ArH), 7.36–7.42 (m, 3H, ArH), 7.46 (t, J=8.0 Hz, 2H, ArH), 7.51 (d, J=7.5 Hz, 1H, ArH), 7.69 (d, J=8.0 Hz, 3H, ArH), 7.74 (br s, 1H, ArH), 8.11 (d, J=7.0 Hz, 1H, ArH), 8.16 (s, 1H, ArH), 8.83 (br s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 121.9, 125.6, 127.0, 127.9, 128.0, 128.1, 128.4, 128.5, 128.8, 128.9, 129.7, 132.1, 135.3, 137.1, 139.4, 146.3, 150.5, 151.6; MS (m/z, %): 394 (M^++1, 100), 393 (M^+, 40). Anal. Calcd for $C_{25}H_{19}N_3S$ (393.50): C, 76.31; H, 4.87; N, 10.68%. Found C, 76.47; H, 4.72; N, 10.53%.

*4.4.10. 3-(Methylthio)-1,4,5-triphenyl-1H-pyrazole (**8a**)*[17]. Yield 83% (0.36 g); white solid; mp 204–205 °C; R_f 0.43 (9:1 hexanes/EtOAc); IR (KBr): 3055, 2923, 1595, 1499, 1445, 1385, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H, SCH_3), 7.03 (d, J=6.8 Hz, 2H, ArH), 7.16–7.27 (m, 13H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 121.4, 124.9, 126.7, 126.9, 128.1, 128.3, 128.4, 128.7, 129.7, 129.8, 130.3, 131.9, 139.8, 140.9, 146.8.

*4.4.11. 4-(4-Methoxyphenyl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8b**).* Yield 84% (0.39 g); white solid; mp 152–154 °C; R_f 0.34 (9:1 hexane/EtOAc); IR (KBr): 3049, 2921, 1506, 1248, 1175, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 6.80 (d, J=8.2 Hz, 2H, ArH), 7.04 (d, J=7.6 Hz, 2H, ArH), 7.13 (d, J=8.5 Hz, 2H, ArH), 7.18–7.28 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 55.0, 113.6, 121.0, 124.2, 124.8, 126.9, 128.2, 128.3, 128.6, 129.9, 130.2, 130.8, 139.8, 140.6, 146.7, 158.3; MS (m/z, %): 373 (M^++1, 100), 372 (M^+, 76). Anal. Calcd for $C_{23}H_{20}N_2OS$ (372.48): C, 74.16; H, 5.41; N, 7.52%. Found C, 73.99; H, 5.21; N, 7.47%.

*4.4.12. 4-(4-Acetylphenyl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8c**).* Yield 68% (0.33 g); white solid; mp 196–197 °C; R_f 0.32 (9.0:1.0 hexanes/EtOAc); IR (KBr): 3053, 2925, 1671, 1600, 1493, 1265, 761, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, SCH_3), 2.53 (s, 3H, $COCH_3$), 6.97 (d, J=7.1 Hz, 2H, ArH), 7.13–7.24 (m, 10H, ArH), 7.77 (d, J=7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 26.5, 120.1, 124.9, 127.2, 128.2, 128.6, 128.69, 128.74, 129.4, 129.5, 130.1, 135.1, 137.2, 139.4, 141.5, 146.8, 197.7; MS (m/z, %): 385 (M^++1, 100), 384 (M^+, 44). Anal. Calcd for $C_{24}H_{20}N_2OS$ (384.49): C, 74.97; H, 5.24; N, 7.29%. Found C, 74.82; H, 5.25; N, 7.31%.

*4.4.13. 3-(Methylthio)-1,5-diphenyl-4-(thiophen-2-yl)-1H-pyrazole (**8d**).* Yield 62% (0.27 g); white solid; mp 188–190 °C; R_f 0.43 (9.2:0.8 hexanes/EtOAc); IR (KBr): 3063, 2930, 1586, 1493, 1365, 763, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H, SCH_3), 6.95 (t, J=4.3 Hz, 1H, ArH), 6.97 (d, J=3.4 Hz, 1H, ArH), 7.17 (d, J=5.6 Hz, 3H, ArH), 7.24–7.32 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 115.2, 124.7, 124.9, 126.5, 126.8, 127.1, 128.5, 128.7, 128.8, 129.6, 130.5, 133.0, 139.6, 141.3, 146.9; MS (m/z, %): 349 (M^++1, 72), 348 (M^+, 62). Anal. Calcd for $C_{20}H_{16}N_2S_2$ (348.48): C, 68.93; H, 4.63; N, 8.04%. Found C, 68.99; H, 4.66; N, 8.00%.

*4.4.14. 4-(Furan-2-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8e**).* Yield 63% (0.26 g); white solid; mp 147–148 °C; R_f 0.40 (9:1 hexanes/EtOAc); IR (KBr): 3061, 2924, 1595, 1497, 1358, 1026, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.57 (s, 3H, SCH_3), 6.13 (d, J=4.4 Hz, 1H, Ar), 6.26 (dd, J=4.3, 2.4 Hz, 1H, Ar), 7.13–7.20 (m, 7H, ArH), 7.21–7.27 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 107.8, 111.2, 112.8, 125.2, 127.5, 128.8, 129.1, 129.2, 130.4, 130.7, 139.9, 141.4, 141.8, 146.8, 147.0; MS (m/z, %): 333 (M^++1, 100), 332 (M^+, 63). Anal. Calcd for $C_{20}H_{16}N_2OS$ (332.42): C, 72.26; H, 4.85; N, 8.43%. Found C, 72.15; H, 4.76; N, 8.52%.

*4.4.15. 4-(Pyridin-3-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8f**).* Yield 62% (0.27 g); yellow solid; mp 163–166 °C; R_f 0.28 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3051, 2922, 1592, 1498, 1380, 1356, 762, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, SCH_3), 7.03 (d, J=7.6 Hz, 2H, ArH), 7.19–7.29 (m, 10H, ArH), 8.44 (br s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 117.8, 123.1, 124.8, 127.2, 128.6, 128.7, 129.1, 130.0, 136.8, 139.4, 141.6, 146.8, 147.6, 150.3; MS (m/z, %): 344 (M^++1, 90), 343 (M^+, 44). Anal. Calcd for $C_{21}H_{17}N_3S$ (343.44): C, 73.44; H, 4.99; N, 12.23%. Found C, 73.51; H, 4.86; N, 12.40%.

*4.4.16. 4-(1-Methyl-lH-indol-5-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8g**).* Yield 72% (0.36 g); white solid; mp 177–178 °C; R_f 0.44 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3057, 2923, 1592, 1500, 1425, 1384, 1355, 766, 732, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H, SCH_3), 3.70 (s, 3H, NCH_3), 6.38 (d, J=3.1 Hz, 1H, ArH), 6.97–7.20 (m, 2H, ArH), 7.04 (dd, J=8.3, 1.7 Hz, 2H, ArH), 7.11–7.20 (m, 5H, ArH), 7.24 (d, J=4.1 Hz, 4H, ArH), 7.50 (d, J=1.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 32.3, 101.1, 108.9, 122.2, 122.5, 122.7, 123.8, 124.9, 126.80, 128.0, 128.2, 128.6, 128.9, 130.1, 130.3, 135.6, 139.9, 140.6, 147.1; MS (m/z, %): 396 (M^++1, 100), 395 (M^+, 82). Anal. Calcd for $C_{25}H_{21}N_3S$ (395.52): C, 75.92; H, 5.35; N, 10.62%. Found C, 76.10; H, 5.45; N, 10.73%.

*4.4.17. 4-(1-Benzenesulfonyl-1H-indol-3-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8h**).* Yield 55% (0.36 g); white solid; mp 168–171 °C; R_f 0.32 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3057, 2925, 1594, 1496, 1444, 1363, 1177, 754, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 6.92 (d, J=7.6 Hz, 2H, ArH), 6.97 (t,

J=7.5 Hz, 1H, ArH), 7.03 (t, J=7.8 Hz, 3H, ArH), 7.12–7.22 (m, 7H, ArH), 7.33 (t, J=7.8 Hz, 2H, ArH), 7.42 (s, 1H, ArH), 7.45 (t, J=7.3 Hz, 1H, ArH), 7.70 (d, J=7.8 Hz, 2H, ArH), 7.88 (d, J=8.3 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 112.4, 113.4, 114.3, 121.0, 123.1, 124.7, 124.9, 125.6, 126.7, 127.2, 128.3, 128.4, 128.8, 129.1, 129.5, 129.7, 130.1, 133.6, 134.9, 137.9, 139.6, 142.2, 148.0; MS (m/z, %): 521 (M^+, 100). Anal. Calcd for $C_{30}H_{23}N_3O_2S_2$ (521.65): C, 69.07; H, 4.44; N, 8.06%. Found C, 68.83; H, 4.46; N, 7.91%.

*4.4.18. 4-(Benzofuran-2-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8i**).* Yield 75% (0.36 g); white solid; mp 182–184 °C; R_f 0.41 (9:1 hexanes/EtOAc); IR (KBr): 3057, 2921, 1591, 1495, 1398, 1005, 755, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H, SCH_3), 6.49 (s, 1H, ArH), 7.08 (t, J=6.1 Hz, 2H, ArH), 7.14–7.21 (m, 7H, ArH), 7.22–7.29 (m, 4H, ArH), 7.38 (dd, J=6.1, 1.7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 103.4, 110.9, 111.7, 120.4, 122.6, 123.5, 124.8, 127.2, 128.3, 128.7, 128.9, 129.7, 130.3, 139.3, 142.0, 147.1, 149.1, 154.1; MS (m/z, %): 383 (M^++1, 97), 382 (M^+, 100). Anal. Calcd for $C_{24}H_{18}N_2OS$ (382.48): C, 75.37; H, 4.74; N, 7.32%. Found C, 75.53; H, 4.66; N, 7.50%.

*4.4.19. 4-(Quinolin-3-yl)-3-(methylthio)-1,5-diphenyl-1H-pyrazole (**8j**).* Yield 80% (0.40 g); white solid; mp 178–180 °C; R_f 0.31 (7.5:2.5 hexanes/EtOAc); IR (KBr): 3045, 2924, 1594, 1495, 1357, 757, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (s, 3H, SCH_3), 7.04 (d, J=8.3 Hz, 2H, ArH), 7.06–7.28 (m, 8H, ArH), 7.48 (t, J=7.1 Hz, 1H, ArH), 7.64 (t, J=8.0 Hz, 1H, ArH), 8.04 (d, J=8.3 Hz, 1H, ArH), 7.72 (d, J=8.0 Hz, 1H, ArH), 8.58 (s, 1H, ArH), 8.11 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 117.6, 124.9, 125.5, 126.8, 127.3, 127.7, 128.7, 128.8, 128.9, 129.1, 129.4, 130.1, 136.1, 139.4, 141.7, 145.9, 147.2, 151.1; MS (m/z, %): 394 (M^++1, 100), 393 (M^+, 55). Anal. Calcd for $C_{25}H_{19}N_3S$ (393.50): C, 76.31; H, 4.87; N, 10.68%. Found C, 76.20; H, 5.01; N, 10.73%.

4.5. General procedure for Raney nickel dethiomethylation of pyrazoles 7a,b,e and 8a,b,e

To a solution of appropriate pyrazole (0.4 mmol) in ethanol (10 mL), Raney nickel (W_4, four times by weight) was added and the suspension was refluxed with stirring for 2–7 h (monitored by TLC). The reaction mixture was filtered through sintered funnel and the residue was washed with ethanol. The filtrate was concentrated in vacuum and passed through small silica gel column using hexane/EtOAc (7.5:2.5) as eluent.

*4.5.1. 1,3,4-Triphenyl-1H-prazole (**9a**).* Ref. 17.

*4.5.2. 4-(4-Methoxyphenyl)-1,3-diphenyl-1H-prazole (**9b**).* Yield 88% (0.11 g); light yellow semisolid; R_f 0.34 (9.0:1.0 hexanes/EtOAc); IR (CH_2Cl_2): 3055, 2928, 1603, 1556, 1499, 1250, 1031, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3), 6.76 (d, J=8.8 Hz, 2H, ArH), 7.15 (d, J=8.8 Hz, 3H, ArH), 7.22 (d, J=7.8 Hz, 3H, ArH), 7.34 (t, J=8.2 Hz, 2H, ArH), 7.51 (dd, J=7.42, 2.4 Hz, 2H, ArH), 7.67 (dd, J=8.5, 1.2 Hz, 2H, ArH), 7.83 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 113.9, 118.8, 122.5, 125.1, 126.2, 127.7, 128.2, 128.3, 129.3, 129.8, 133.2, 139.9, 150.2, 158.6; MS (m/z, %): 394 (M^++1, 100), 393 (M^+, 55). Anal. Calcd for $C_{22}H_{18}N_2O$ (326.39): C, 80.96; H, 5.56; N, 8.58%. Found C, 80.70; H, 5.51; N, 8.72%.

*4.5.3. 4-(Furan-2-yl)-1,3-diphenyl-1H-prazole (**9e**).* Yield 76% (0.09 g); viscous semisolid; R_f 0.32 (9:1 hexanes/EtOAc); IR (CH_2Cl_2): 3062, 1599, 1535, 1504, 1452, 1394, 756, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 6.23 (d, J=3.4 Hz, 1H, ArH), 6.37 (dd, J=3.4, 2.0 Hz, 1H, ArH), 7.27–7.49 (m, 7H, ArH), 7.70 (d, J=8.8 Hz, 2H, ArH), 7.78 (d, J=8.8 Hz, 2H, ArH), 8.19 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 106.3, 111.0, 113.7, 118.9, 125.6, 126.5, 128.3, 128.4, 128.5, 129.4, 133.0, 139.6, 141.1, 147.1, 150.1; MS (m/z, %): 287 (M^++1, 100). Anal. Calcd For $C_{19}H_{14}N_2O$ (286.33): C, 79.70; H, 4.93; N, 9.78%. Found C, 79.81; H, 4.87; N, 9.86%.

*4.5.4. 1,4,5-Triphenyl-1H-prazole (**10a**).* Ref. 17.

*4.5.5. 4-(4-Methoxyphenyl)-1,5-diphenyl-1H-prazole (**10b**).* Yield 96% (0.12 g); white solid; mp 150–151 °C (lit. 151 °C);[30] R_f 0.30 (9:1 hexanes/EtOAc); IR (KBr): 3054, 2923, 1512, 1377, 1246, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3), 6.72 (d, J=8.5 Hz, 2H, ArH), 7.05–7.08 (m, 4H, ArH), 7.15–7.24 (m, 8H, ArH), 7.79 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.1, 113.9, 122.1, 125.1, 127.1, 128.3, 128.5, 128.7, 129.1, 130.2, 130.4, 138.7, 139.6, 139.9, 158.2; MS (m/z, %): 327 (M^++1, 100), 326 (M^+, 34). Anal. Calcd for $C_{22}H_{18}N_2O$ (326.39): C, 80.96; H, 5.56; N, 8.58%. Found C, 80.91; H, 5.41; N, 8.67%.

*4.5.6. 4-(2-Furyl)-1,5-diphenyl-1H-pyrazole (**10e**).* Yield 81% (0.09 g); white solid, mp 156–157 °C; R_f 0.31 (9:1 hexane/EtOAc); IR (KBr): 3062, 2956, 1627, 1496, 1445, 1380, 960, 762, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 5.95 (dd, J=2.6, 0.7 Hz, 1H, ArH), 6.29 (dd, J=2.6, 1.6 Hz, 1H, ArH), 7.21–7.29 (m, 7H, ArH), 7.35–7.38 (m, 4H, ArH), 8.02 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 104.7, 110.9, 114.3, 124.8, 127.2, 128.5, 128.6, 128.83, 128.84, 130.0, 130.3, 138.2, 139.6, 140.9, 147.6; MS (m/z %): 287 (M^++1, 100). Anal. Calcd for $C_{19}H_{14}N_2O$ (286.33): C, 79.70; H, 4.93; N, 9.78%. Found C, 79.63; H, 5.04; N, 9.83%.

4.6. General procedure for Sonogashira cross-coupling of 4-iodopyrazoles 5b and 6b with phenylacetylene

A mixture of 4-iodopyrazole **5b** or **6b** (1.27 mmol), phenylacetylene (1.68 mmol), $PdCl_2(PPh_3)_2$ (26.6 mg, 0.038 mmol), CuI (7.2 mg, 0.038 mmol), and K_2CO_3 (0.60 g, 3.8 mmol) in degassed DMF (8.0 mL) was heated at 100 °C for 10 h (monitored by TLC). The reaction mixture was allowed to cool to room temperature and was filtered on Buchner funnel to remove K_2CO_3. Residue was washed with chloroform (2×10 mL). The filtrate was diluted with 75 mL of water and was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with water (2×50 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give products, which were purified by column chromatography over silica gel using hexane/EtOAc (9:1) as eluent.

*4.6.1. 5-(Methylthio)-1,3-diphenyl-4-phenylethynyl-1H-prazole (**12**).* Yield 64% (0.30 g); colorless solid; mp 101 °C; R_f 0.42 (9:1 hexanes/EtOAc); IR (KBr): 3065, 2926, 1592, 1491, 1446, 1372, 975, 757, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, SCH_3), 7.24–7.32 (m, 4H, ArH), 7.34–7.37 (m, 2H, ArH), 7.41 (t, J=8.2 Hz, 3H, ArH), 7.46 (dd, J=7.5, 1.4 Hz, 2H, ArH), 7.54 (d, J=8.01 Hz, 2H, ArH), 96.07, 8.13 (dd, J=7.8, 1.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 81.5, 96.1, 107.1, 123.4, 125.5, 126.9, 128.2, 128.4, 128.5, 128.8, 131.2, 132.2, 139.0, 139.9, 152.1; MS (m/z, %): 367 (M^++1, 100), 366 (M^+, 67). Anal. Calcd for $C_{24}H_{18}N_2S$ (366.48): C, 78.66; H, 4.95; N, 7.64%. Found C, 78.81; H, 4.78; N, 7.48%.

*4.6.2. 3-(Methylthio)-1,5-diphenyl-4-phenylethynyl-1H-prazole (**13**).* Yield 66% (0.31 g); colorless solid; mp 156–157 °C; R_f 0.4 (9:1 hexanes/EtOAc); IR (KBr): 3055, 2930, 2210, 1592, 1494, 1399, 752, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, SCH_3), 7.22–7.26 (m, 8H, ArH), 7.28–7.29 (m, 3H, ArH), 7.34–7.36 (m, 2H, ArH), 7.38–7.40 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 80.2, 94.6, 104.3, 123.3, 124.9, 127.5, 127.9, 128.1, 128.3, 128.6, 128.8, 129.3, 131.1, 139.4, 145.1, 150.6; MS (m/z, %): 367 (M^++1, 100), 366

(M^+, 63). Anal. Calcd for $C_{24}H_{18}N_2S$ (366.48): C, 78.66; H, 4.95; N, 7.64%. Found C, 78.80; H, 4.87; N, 7.71%.

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Supplementary data

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26. Decreasing the catalytic loading of $Pd(PPh_3)_4$ to 5 mol % in the cross-coupling of **5a** with boronic acid **11a** resulted in lower yield of **7a** (52%) under similar reaction conditions.
27. The structures of regioisomeric pyrazoles were further confirmed by X-ray crystallographic data of isomeric 1,3-diphenyl-4-(2-thienyl)-5-methylthio and 1,5-diphenyl-4-(2-thienyl)-3-methylthio-pyrazoles **7d** and **8d**. The CCDC deposition number of **7d** is 806142; molecular formula $C_{20}H_{16}N_2S_2$, chemical formula weight 348.49, monoclinic, unit cell parameters: a=6.086 (3), b=7.444 (5), c=18.675 (4), α=90, β=94.440 (5), γ=90, space group $P21$. The CCDC deposition number of **8d** is 806143; molecular formula $C_{20}H_{16}N_2S_2$, chemical formula weight 348.49, monoclinic, unit cell parameters: a=5.722 (2), b=8.231 (3), c=17.850 (7), α=90, β=99.192 (7), γ=90, space group $P1c1$. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).
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