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Regioselective Synthesis of 1-Aryl-3,4-substituted/annulated-5-(methylthio)pyrazoles and 1-Aryl-3-(methylthio)-4,5-substituted/annulated Pyrazoles[§]

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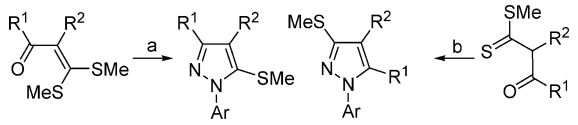

a, $ArNHNH_2$/ *t*-BuOK/ *t*-BuOH/ Δ ; b, $ArNHNH_2$/ EtOH/ Δ

Highly efficient and regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methylthio)-pyrazoles and 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles has been reported via cyclocondensation of arylhydrazines with either α-oxoketene dithioacetals or *β*-oxodithioesters.

Introduction

Synthesis of pyrazole and its *N*-aryl analogues has been a subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as in agrochemical industry.[1,2] Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, antiinflammatory, antipyretic, antibacterial, and sedative-hypnotic activity.[2d−f] The 1-phenylpyrazole motif is present in several drug candidates for treatment of various diseases such as cyclooxygenase-2 (Cox-2) inhibitors, IL-1 synthesis inhibitors, and protein kinase inhibitors etc.[3] Similarly a few of the 1,5-diarylpyrazole derivatives have been shown to exhibit nonnucleoside HIV-1 reverse transcriptase inhibitory activities[4] along with Cox-2 inhibitor.[2g−h] The corresponding 1,3,5-triaryl-4-alkylpyrazoles have been recently identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficacy for ERα subtype.[5] Therefore continuous efforts have been devoted to the development of more general, efficient, and regioselective methods for the synthesis of this class of compounds.

One of the most important methods for the synthesis of substituted 1-*N*-arylpyrazoles involves cyclocondensation of 1,3-dicarbonyl compounds and their equivalent 1,3-dienophilic synthons such as propargylic ketones[6] or

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[§] Dedicated to Dr. Nitya Nand on his 80th birthday.

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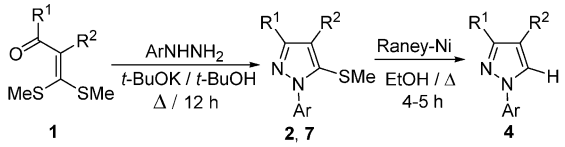
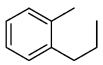
β-dialkylamino/alkoxy/chloro ketones[7] with arylhydrazines.[2,8] However the appealing generality of this method is somewhat vitiated due to frequent formation of a regioisomeric mixture of unsymmetrical pyrazoles in these reactions.[5a,9] Therefore several elegant methods for the regioselective synthesis of unsymmetrically substituted 1-arylpyrazoles have been reported in the literature.[2,3,5a,6a,10]

During the course of our ongoing interest in development of efficient general synthetic routes for five- and six-membered heterocycles utilizing α-oxoketene dithioacetals as versatile three-carbon building blocks,[11] we have shown in earlier studies that it is possible to tune the reactivity of these ambident electrophiles toward unsymmetrical heterobinucleophiles and 1,3-carbanionic species by variation of reaction conditions to afford substituted five-/six-membered heterocycles,[12] aromatic[11,13] and heteroaromatic[11c,14] compounds in highly regiocontrolled fashion. In continuation of these studies, we now report regioselective synthesis of isomeric 1-aryl-3,4-substituted-5-(methylthio) (**2**) and 1-aryl-3-(methylthio)-4,5-substituted (**3**) pyrazoles by reaction of arylhydrazines with either α-oxoketene dithioacetals or β-oxodithioesters, respectively. There are a few reports on the reactions of α-oxo[15a−e] or doubly activated ketene dithioacetals[15f−l] with phenyl and methylhydrazines yielding either of the regioisomeric pyrazoles or the mixture of both; however, no attempts have been made to address the regiochemical issue associated with this heterocyclization reaction.

TABLE 1. Synthesis of 1-Aryl-3,4-substituted/annulated-5-(methylthio)pyrazoles



1 **2, 7** **4**

Entry	1, 2, 4, 7	Ar	%Yield 2	%Yield 4
1	**1a**, **2a**, **4a**, $R^1 = C_6H_5$; R^2 = H	C_6H_5	98%	98%
2	**1b**, **2b**, R^1 = 4-ClC_6H_4; R^2 = H	C_6H_5	70%	-
3	**1c**, **2c**, R^1 = 4-MeOC_6H_4; R^2 = H	C_6H_5	94%	-
4	**1d**, **2d**, **4d**, $R^1 = R^2 = C_6H_5$	C_6H_5	80%	93%
5	**1e**, **2e**, R^1 = 3-Py; $R^2 = C_6H_5$	C_6H_5	85%	-
6	**1f**, **2f**, **4f**, R^1 = Me; R^2 = H	C_6H_5	96%	91%
7	**1g**, **2g**, R^1 = *i*-Pr; R^2 = H	C_6H_5	71%	-
8	**1h**, **2h**, $R^1 = CH(OMe)_2$; R^2 = H	C_6H_5	*a*	
	8, R^1 = CHO; R^2 = H	C_6H_5	77%[b]	-
	$R^1 = R^2 =$ 			
9	**1i**, **2i**, **4i**, **n = 2**	C_6H_5	90%	95%
10	**1j**, **2j**, **n = 1**	C_6H_5	51%	-
11	**1k**, **2k**, **4k**, $R^1 = R^2 = -(CH_2)_4-$	C_6H_5	79%	91%
12	**1a, 7a**, $R^1 = C_6H_5$; R^2 = H	4-FC_6H_4	76%	-
13	**1d, 7d**, $R^1 = R^2 = C_6H_5$	4-FC_6H_4	80%	-
14	**1i**, **7i**, $R^1 = R^2 =$ 	4-FC_6H_4	88%	-

[a] Not isolated. [b] Obtained by in situ acidic hydrolysis of **2h**.

Results and Discussion

The reaction of α-benzoylketene dithioacetal **1a** with phenylhydrazine was first investigated under a variety of reaction conditions (neutral, acidic, basic). Best results were obtained when the reaction was conducted in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, furnishing only one regioisomeric pyrazole **2a** in high yield (Table 1, entry 1). The structure of **2a** was established on the basis of its reported[16] physical and spectral data, and also by its Raney-Ni dethiomethylation to the known 1,3-diphenylpyrazole **4a**.[17] Also the pyrazole **4a** could be synthesized by an alternate route through $BF_3 \cdot Et_2O$ induced cyclization of the phenylhydrazone **6a** from β-oxodithioacetal **5a** which unequivocally confirmed the regiochemical assignment of the pyrazole **2a** (Scheme 1).

The generality of the reaction was demonstrated by the synthesis of other substituted 1,3-diaryl-5-(methylthio)-pyrazoles **2b,c** (Table 1, entries 2 and 3), 1,3,5-triaryl/heteroaryl-5-(methylthio)pyrazoles **2d,e** (entries 4 and 5), and the corresponding 1-aryl-3-alkyl-5-(methylthio)pyrazoles **2f,g** (entries 6 and 7) in high yields from the

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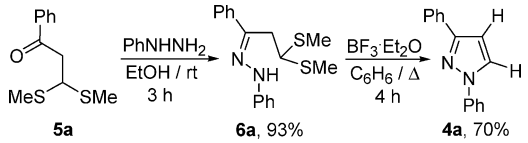
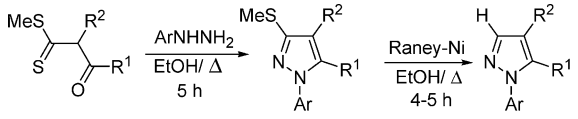
SCHEME 1

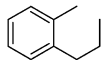


respective ketene dithioacetals under identical conditions. The corresponding 3-formyl-1-phenyl-5-(methylthio)pyrazole (**8**) could also be prepared in 77% yield by in situ acidic hydrolysis of 3-bis(methoxy)methylpyrazole **2h** obtained from the ketene dithioacetal **1h** and phenylhydrazine under these conditions (entry 8). The cyclocondensation protocol was found to be equally facile with cyclic α-oxoketene dithioacetals **1i** and **1k** from 1-tetralone and cyclohexanone yielding the respective 1-aryl-3,4-annulated pyrazoles **2i** and **2k** in high yields as single regioisomers under identical conditions (entries 9 and 11). On the other hand, the 3,4-indano fused pyrazole **2j** was obtained from **1j** only in moderate yield of 51% (entry 10). The reaction of ketene dithioacetals **1a**, **1d**, and **1i** with 4-fluorophenylhydrazine also afforded the respective 1-(4-fluorophenyl)pyrazoles **7a**, **7d**, and **7i** in overall good yields (entries 12−14). The structures and regiochemistry of all newly synthesized 1-arylpyrazoles were confirmed with the help of spectral and analytical data and also by desulfurization of pyrazoles **2d**, **2f**, **2i**, and **2k** to the known pyrazoles **4d**,[18] **4f**,[19] **4i**,[20] and **4k**[21] in high yields (entries 4, 6, 9, and 11).

After having accomplished the regiospecific synthesis of 1-aryl-3,4-substituted/annulated 5-(methylthio)-pyrazoles **2** (Table 1), we focused our attention toward synthesis of regioisomeric 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles **3** from the same α-oxoketene dithioacetal precursors by variation of reaction conditions. However, our various attempts to procure the pyrazole **3a** by reacting the ketene dithioacetal **1a** with phenylhydrazine under neutral, mild acidic, or basic conditions led to only frustrating results, yielding either the starting material along with the pyrazole **2a** or the inseparable mixture of pyrazoles **2a** and **3a**. On the other hand, in a parallel study, we diverted our attention to β-oxodithioesters,[22] which are reported to react with hydrazine hydrate to afford 3(5)-aryl-5(3)-thiopyrazoles in good yields.[23] We therefore examined the reaction of β-oxodithioester **9a** ($R^1 = C_6H_5$, $R^2 = H$) with phenylhydrazine in refluxing ethanol, yielding a single product (81%), which to our surprise was found to be the desired regioisomeric 1,5-diphenyl-3-(methylthio)pyrazole (**3a**) formed by elimination of H_2S instead of methylmercaptan (Table 2, entry 1). The structure of **3a** was established with the help of spectral and analytical data and also by its Raney-Ni dethiomethylation to the known 1,5-diphenylpyrazole **10a**.[17]

TABLE 2. Synthesis of 1-Aryl-4,5-substituted/annulated-3-(methylthio)pyrazoles



Entry	2, 3, 9, 10, 11	Ar	%Yield 3	%Yield 10
1	**9a**, **3a**, **10a**, $R^1 = C_6H_5$; $R^2 = H$	C_6H_5	81%	88%
2	**9b**, **3b**, $R^1 = 4\text{-}ClC_6H_4$; $R^2 = H$	C_6H_5	68%	-
3	**9c**, **3c**, $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$	C_6H_5	80%	-
4	**9d**, **3d**, **10d**, $R^1 = R^2 = C_6H_5$	C_6H_5	75%	95%
5	**9e**, **3e**, R^1 = 3-Py; $R^2 = C_6H_5$	C_6H_5	69%	-
6	**9f**, **3f**, **10f**, R^1 = Me; $R^2 = H$	C_6H_5	45%	85%
7	**9g**, **3g**, R^1 = *i*-Pr; $R^2 = H$	C_6H_5	45%	-
8	**9h**, **2h**, $R^1 = CH(OMe)_2$; $R^2 = H$	C_6H_5	*a*	
	8, $R^1 = CHO$; $R^2 = H$	C_6H_5	*b*	-
	$R^1 = R^2 =$ 			
9	**9i**, **3i**, **10i**, **n = 2**	C_6H_5	70%	91%
10	**9j**, **n = 1**	C_6H_5	*c*	-
11	**9k**, $R^1 = R^2 = -(CH_2)_4-$	C_6H_5	*d*	*e*
12	**9a**, **11a**, $R^1 = C_6H_5$; $R^2 = H$	$4\text{-}FC_6H_4$	69%	-
13	**9d**, **11d**, $R^1 = R^2 = C_6H_5$	$4\text{-}FC_6H_4$	88%	-
14	**9i**, **11i**, $R^1 = R^2 =$ 	$4\text{-}FC_6H_4$	72%	-

[a] Not isolated. [b] Product **8**, 51% obtained by in situ acidic hydrolysis of **2h**. [c] Product **2j**, 51%. [d] Product **2k**, 61%. [e] Product **4k**, 90%.

The generality of the reaction was established by synthesis of regioisomeric pyrazoles **3b**−**e** in high yields by cyclocondensation of the appropriate β-oxodithioesters **9b**−**e** with phenylhydrazine under identical conditions (entries 2−5). However the corresponding acyldithioesters **9f,g** (R = Me, isopropyl) gave the respective 5-alkyl-3-(methylthio)pyrazoles **3f,g** in lower yields (entries 6 and 7). The cyclic β-ketodithioester **9i** from 1-tetralone was also smoothly converted to the 4,5-dihydrobenzo[*g*]indazole **3i** when reacted with phenylhydrazine under similar conditions (entry 9). On the other hand, the cyclocondensation of β-oxodithioesters **9h** and **9j,k** derived from pyruvaldehyde dimethylacetal, 1-indanone, and cyclohexanone, respectively, with phenylhydrazine under refluxing ethanol yielded only the 3-formyl-1-phenyl-5-(methylthio)pyrazole (**8**) (after in situ acidic hydrolysis) and the 3,4-annulated-5-(methylthio)-pyrazoles **2j,k**, identical with those obtained earlier from the reaction of α-oxoketene dithioacetals **1h** and **1j,k** with phenylhydrazine (Table 2, entries 8, 10, and 11). The corresponding 1-(4-fluorophenyl)pyrazoles **11a**, **11d**, and **11i** were also obtained in good yields when the β-ketodithioesters **9a**, **9d**, and **9i** were reacted with 4-fluorophenylhydrazine under identical conditions (entries 12−14). The structures of all newly synthesized regioisomeric pyrazoles **3b**−**g,i** and **11a,d,i** were established with the help of spectral and analytical data and also by Raney-Ni

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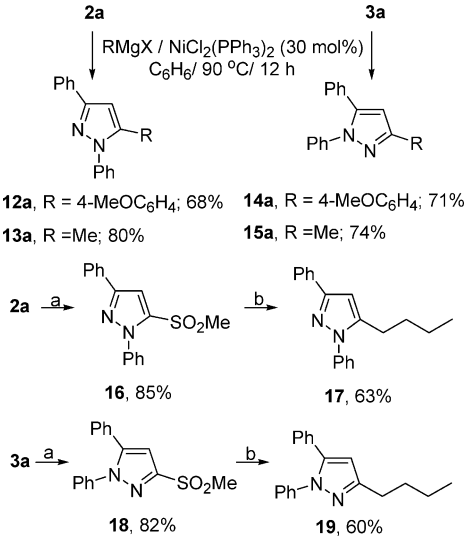
SCHEME 2[a]



[a] (a) *m*-CPBA (2.2 equiv)/DCM/0−rt/4 h; (b) *n*-BuMgBr/$NiCl_2$-(dppp) (30 mol %)/C_6H_6/90 °C/12 h.

desulfurization of **3d**, **3f**, and **3i** to the known pyrazoles **10d**,[18] **10f**,[19] and **10i**,[24] respectively (entries 4, 6, and 9).

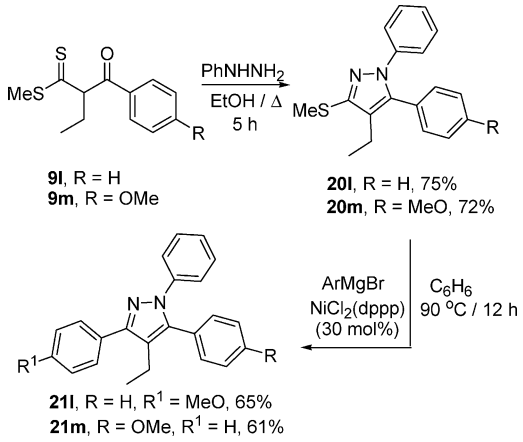
With a number of regioisomeric 5- and 3-(methylthio)pyrazoles in hand, we further contemplated to elaborate methylthio functionality in these pyrazoles, for the synthesis of regiospecific alkyl/aryl-substituted pyrazoles as shown in Scheme 2. Thus the nickel-catalyzed cross-coupling[25] of the pyrazoles **2a** and **3a** with 4-methoxyphenyl Grignard reagent afforded the corresponding 1,3-diphenyl-5-(4′-methoxyphenyl)- and 1,5-diphenyl-3-(4′-methoxyphenyl)pyrazoles **12a** and **14a** in good yields (Scheme 2). Similarly the corresponding 1,3-diphenyl-5-methyl- and 1,5-diphenyl-3-methylpyrazoles **13a** and **15a** were obtained in 80% and 74% yields, respectively, by treatment of pyrazoles **2a** and **3a** with methylmagnesium iodide in the presence of $NiCl_2(PPh_3)_2$ catalyst (Scheme 2). On the other hand, the corresponding regioisomeric 5- or 3-(*n*-butyl)pyrazoles **17** and **19** were obtained by nickel-catalyzed cross-coupling reaction of *n*-butyl Grignard reagent with the respective 5- or 3-(methylsulfonyl)-pyrazoles **16** and **18** obtained by *m*-CPBA oxidation of **2a** and **3a**, respectively (Scheme 2).

This strategy was applied for the synthesis of regioisomeric 1,3,5-triaryl-4-ethylpyrazoles **21l,m,** which are shown to be high affinity binding and selective estrogen receptor (ER) ligands for ERα subtype (ERα).[5] Thus the reaction of dithioesters **9l,m** with phenylhydrazine afforded the corresponding 1,5-diaryl-4-ethyl-3-(methylthio)-pyrazoles **20l,m** in high yields. Subsequent nickel-catalyzed cross-coupling of **20l,m** with either 4-methoxyphenyl or phenyl Grignard reagents, respectively, afforded the isomeric pyrazoles **21l,m** in good yields (Scheme 3).

Conclusion

In summary, we have developed an efficient general synthesis of 1-aryl-3,4-substituted-5-(methylthio)-pyrazoles and 1-aryl-3-(methylthio)-4,5-subsituted pyrazoles from two regiospecific processes, namely, the cyclocondensation of arylhydrazines with α-oxoketene dithioacetals and *β*-oxodithioesters, respectively, with both precursors easily accessible from active methylene ketones.[11,22a] The 3- and 5-methylthio (or methylsulfonyl) functionalities in these isomeric pyrazoles can be further elaborated for regiospecific introduction of either 3/5-alkyl or -aryl groups via nickel-catalyzed cross-coupling with the respective Grignard reagents, which has also been applied for regioselective synthesis of pyrazoles **21l,m** as ligands for estrogen receptor. The overall study suggests the possibility of extension of these protocols for generation of large number of 1-arylpyrazoles in a highly regiocontrolled fashion for biological screening. Our efforts in this direction and to probe the mechanism of these regioselective cyclizations are in progress.

SCHEME 3



Experimental Section

General details are described in Supporting Information. All known α-oxoketene dithioacetals **1a**−**k**, *β*-oxodithioesters **9a**−**k**, and unknown *β*-oxodithioesters **91,m** were prepared by reported procedure.[11,22a] 3,3-Bis(methylthio)-1-phenyl-propan-1-one **5a** was prepared by reported procedure.[26]

General Procedure for Preparation of 1-Aryl-3,4-substituted/annulated-5-(methylthio)pyrazoles 2, 7. In a typical experiment a solution of respective α-oxoketene dithioacetal **1** (5 mmol), arylhydrazine (6 mmol), and *t*-BuOK (1.12 g, 10 mmol) in 50 mL of *t*-BuOH was refluxed for 10−12 h with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure, poured into ice-cold water, extracted with CH_2Cl_2 (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **2** or **7**, which were purified by column chromatography over silica gel using hexane−EtOAc (10:1) as eluent.

1,3-Diphenyl-5-(methylthio)-1*H*-pyrazole (2a).[16] Yield 98% (1.30 g); pale yellow viscous liquid; R_f 0.57 (9.2:0.8 hexanes−EtOAc). IR (CH_2Cl_2): 3060, 2922, 1597, 1525, 1499, 1456, 1412, 1362, 1316 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.94 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.45−7.53 (m, 4H), 7.35−7.40 (m, 2H), 6.69 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 152.2, 139.6, 139.1, 132.9, 129.1, 128.7, 128.2, 127.9, 125.7, 124.8, 105.4, 18.1. MS (*m/z*, %): 267 (M +

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1, 100). Anal. Calcd for $C_{16}H_{14}N_2S$ (266.37): C, 72.15; H, 5.30; N, 10.52. Found: C, 72.05; H, 5.18; N, 10.45.

1-(4′-Fluorophenyl)-3,4-diphenyl-5-(methylthio)-1*H*-pyrazole (7d). Yield 80% (1.44 g); colorless solid; mp 91−92 °C; R_f 0.43 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3060, 2926, 1602, 1506, 1433, 1376, 1347 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (ddd, J = 6.8, 4.6, 2.2 Hz, 2H), 7.46−7.48 (m, 2H), 7.33−7.38 (m, 5H), 7.23−7.26 (m, 3H), 7.19 (t, J = 8.5 Hz, 2H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J = 246.8), 150.1, 135.8, 134.5, 132.7, 132.6, 130.4, 128.3, 128.2, 128.0, 127.8, 127.5 (d, J = 8.2 Hz), 127.3, 125.8, 115.7 (d, J = 23.0 Hz), 18.7. MS (*m/z*, %): 361 (M + 1, 100), 360 (M$^+$, 70). Anal. Calcd for $C_{22}H_{17}FN_2S$ (360.45): C, 73.31; H, 4.75; N, 7.77. Found: C, 73.42; H, 4.89; N, 7.95.

3-Isopropyl-5-(methylthio)-1-phenyl-1*H*-pyrazole (2g). Yield 71% (0.82 g); yellow liquid; R_f 0.65 (9.2:0.8 hexanes−EtOAc). IR (CH_2Cl_2): 2962, 2925, 1596, 1507, 1458, 1424, 1371 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dt, J = 7.2, 1.2 Hz, 2H), 7.42 (dt, J = 7.2, 2.0 Hz, 2H), 7.29−7.34 (m, 1H), 6.17 (s, 1H), 3.02 (sept, J = 7.2 Hz, 1H), 2.34 (s, 3H), 1.29 (d, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 139.6, 137.5, 128.8, 127.4, 124.6, 104.9, 27.9, 22.7, 17.9. MS (*m/z*, %): 233 (M + 1, 100), 232 (M$^+$, 50). Anal. Calcd for $C_{13}H_{16}N_2S$ (232.34): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.11; H, 7.01; N, 12.17.

General Procedure for Preparation of 1-Aryl-3-(methylthio)-4,5-substituted/annulated Pyrazoles 3, 11. A solution of respective β-oxodithioesters **9** (5 mmol) and arylhydrazine (6 mmol) in 50 mL of EtOH was heated at refluxed for 5−6 h with constant stirring, the reaction being monitored by TLC. The solvent was removed under reduced pressure and poured into ice-cold water, extracted with DCM (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **3** and **11**, which were purified by column chromatography over silica gel using hexane−EtOAc (10:1) as eluent.

1,5-Diphenyl-3-(methylthio)-1*H*-pyrazole (3a). Yield 81% (1.08 g); colorless solid; mp 59−60 °C; R_f 0.57 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3063, 2927, 1597, 1539, 1499, 1451, 1419, 1364, 1317 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.26 (m, 8H), 7.15−7.18 (m, 2H), 6.39 (s, 1H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 144.3, 139.7, 130.0, 128.8, 128.6, 128.4, 128.3, 127.2, 124.9, 107.5, 15.7. MS (*m/z*, %): 267 (M + 1, 100), 266 (M$^+$, 40). Anal. Calcd for $C_{16}H_{14}N_2S$ (266.37): C, 72.15; H, 5.30; N, 10.52. Found: C, 72.24; H, 5.22; N, 10.43.

1-(4′-Fluorophenyl)-4,5-diphenyl-3-(methylthio)-1*H*-pyrazole (11d). Yield 88% (1.58 g); white solid; mp 145−147 °C; R_f 0.64 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3259, 3059, 2924, 1604, 1509, 1444, 1385, 1267, 1227 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.31 (m, 10H), 7.06 (d, J = 7.7 Hz, 2H), 6.99 (dt, J = 7.7, 2.2 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (d, J = 246 Hz), 146.9, 141.1, 135.9, 131.8, 130.2, 129.6, 129.5, 128.5 (× 2C), 128.2, 126.7 (d, J = 6.6 Hz), 126.6, 121.3, 115.6 (d, J = 23.0 Hz), 15.0. MS (*m/z*, %): 361 (M + 1, 100), 360 (M$^+$, 60). Anal. Calcd for $C_{22}H_{17}FN_2S$ (360.45): C, 73.31; H, 4.75; N, 7.77. Found: C, 73.22; H, 4.64; N, 7.89.

5-Isopropyl-3-(methylthio)-1-phenyl-1*H*-pyrazole (3g). Yield 45% (0.52 g); orange liquid; R_f 0.58 (9.2:0.8 hexanes−EtOAc). IR (CH_2Cl_2): 2966, 2927, 1595, 1527, 1500, 1453, 1358 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.45 (m, 5H), 6.13 (s, 1H), 2.97 (sept, J = 6.8 Hz, 1H), 2.51 (s, 3H), 1.14 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 147.4, 139.5, 129.1, 128.1, 125.8, 102.9, 25.5, 22.8, 15.6. MS (*m/z*, %): 233 (M + 1, 100), 232 (M$^+$, 90). Anal. Calcd for $C_{13}H_{16}N_2S$ (232.34): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.31; H, 6.81; N, 12.15.

General Procedure for Nickel-Catalyzed Cross-Coupling Reactions of 2a and 3a with Grignard Reagents. Synthesis of 12a, 13a, 14a, and 15a. A solution of respective Grignard reagent (0.10 mmol) in Et_2O was added dropwise to a stirring suspension of $(Ph_3P)_2NiCl_2$ (0.2 g, 30 mol %) in 25 mL of dry benzene under a nitrogen atmosphere, and the mixture was refluxed for 15 min. After the catalyst reduction, 1.90 mmol of the required Grignard reagent (4-$MeOC_6H_4MgBr$/MeMgI) and a solution of pyrazoles **2a** or **3a** (1.0 mmol) in dry benzene (20 mL) were added to the reaction mixture and refluxed for 12 h. It was then cooled, poured into 50 mL of saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and evaporated to give crude products **12a** and **13a** or **14a** and **15a**, which were purified by column chromatography using hexane−EtOAc as eluent.

1,3-Diphenyl-5-(4′-methoxyphenyl)-1*H*-pyrazole (12a). Yield 68% (0.22 g); yellow viscous liquid (lit. 77−78 °C);[27] R_f 0.41 (9.2:0.8 hexanes−EtOAc). IR (CH_2Cl_2): 3052, 2929, 1612, 1519, 1495, 1458, 1361, 1293, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd J = 6.7, 2.0 Hz, 2H), 7.29−7.35 (m, 4H), 7.19−7.24 (m, 4H), 7.09 (dd, J = 6.8, 2.0 Hz, 2H), 6.74 (dd, J = 6.8, 2.0 Hz, 2H), 6.67 (s, 1H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 151.8, 144.2, 140.2, 133.1, 129.9, 128.9, 128.6, 127.9, 127.3, 125.8, 125.3, 122.9, 113.9, 104.7, 55.2. MS (*m/z*, %): 327 (M + 1, 100), 326 (M$^+$, 60). Anal. Calcd for $C_{22}H_{18}N_2O$ (326.39): C, 80.96; H, 5.56; N, 8.58. Found: C, 81.07; H, 5.63; N, 8.46.

1,5-Diphenyl-3-(4′-methoxyphenyl)-1*H*-pyrazole (14a). Yield 71% (0.23 g); colorless solid; mp 132−133 °C (lit. 138 °C);[5,28] R_f 0.38 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3055, 2839, 1603, 1494, 1445, 1352, 1292, 1248 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.6 Hz, 2H), 7.25−7.35 (m, 10H), 6.96 (d, J = 8.6 Hz, 2H), 6.75 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 151.8, 144.3, 140.1, 130.6, 128.9, 128.7, 128.4, 128.2, 127.3, 127.0, 125.8, 125.2, 113.9, 104.8, 55.3. MS (*m/z*, %): 327 (M + 1, 100), 326 (M$^+$, 90). Anal. Calcd for $C_{22}H_{18}N_2O$ (326.39): C, 80.96; H, 5.56; N, 8.58. Found: C, 80.85; H, 5.65; N, 8.67.

Procedure for Preparation of 1,5-Diphenyl-4-ethyl-3-(methylthio)-1*H*-pyrazole (20l) and 4-Ethyl-5-(4-methoxyphenyl)-3-(methylthio)-1-phenyl-1*H*-pyrazole (20m). A solution of β-oxodithioesters **9l** or **9m** (5 mmol) and phenylhydrazine (0.65 g, 6 mmol) in 50 mL of EtOH was refluxed for 5 h with constant stirring (monitored by TLC). The solvent was removed under reduced pressure and poured into ice-cold water, extracted with CH_2Cl_2 (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **20l,m**, which were purified by column chromatography over silica gel using hexane−EtOAc (10:1) as eluent.

1,5-Diphenyl-4-ethyl-3-(methylthio)-1*H*-pyrazole (20l). Yield 75% (1.10 g); colorless solid; mp 66−67 °C; R_f 0.45 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3065, 2958, 2921, 1593, 1498, 1435, 1393, 1354 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.37 (m, 3H), 7.23−7.28 (m, 3H), 7.18−7.23 (m, 4H), 2.65 (s, 3H), 2.49 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 140.8, 139.9, 130.6, 129.8, 128.6, 128.5, 128.3, 126.5, 124.4, 122.5, 16.9, 15.6, 15.2. MS (*m/z*, %): 295 (M + 1, 100), 294 (M$^+$, 90). Anal. Calcd for $C_{18}H_{18}N_2S$ (294.41): C, 73.43; H, 6.16; N, 9.51. Found: C, 73.52; H, 6.26; N, 9.43.

4-Ethyl-5-(4′-methoxyphenyl)-3-(methylthio)-1-phenyl-1*H*-pyrazole (20m). Yield 72% (1.17 g); red viscous liquid; R_f 0.47 (9.2:0.8 hexanes−EtOAc). IR (CH_2Cl_2): 2963, 2927, 1612, 1597, 1575, 1505, 1459, 1433, 1391, 1353, 1289, 1176 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.29 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H), 2.66 (s, 3H), 2.46 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 146.6, 140.9, 139.5, 131.0, 129.7, 126.7, 124.6, 122.4, 122.3, 114.0, 55.2, 16.9, 15.8, 15.1. MS (*m/z*, %): 325 (M + 1, 100), 324 (M$^+$, 40). Anal. Calcd for

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$C_{19}H_{20}N_2OS$ (324.44): C, 70.34; H, 6.21; N, 8.63. Found: C, 70.45; H, 6.13; N, 8.51.

Procedure for Synthesis of Regioisomeric 1,3,5-Triaryl-4-ethylpyrazoles 21l,m. A solution of respective Grignard reagent (0.05 mmol) in Et_2O was added dropwise to a stirring suspension of $NiCl_2$(dppp) (0.08 g, 30 mol %) in 15 mL of dry benzene under argon atmospher,e and the mixture was refluxed for 15 min. After the catalyst reduction, 0.95 mmol of the required Grignard reagent (PhMgBr/4-$MeOC_6H_4MgBr$) and a solution of pyrazoles **20l** or **20m** (0.5 mmol) in dry benzene (15 mL) were added to the reaction mixture and refluxed for 12 h. It was then cooled, poured into 30 mL of saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried (anhydrous Na_2SO_4) and evaporated to give crude products **21l** or **21m**, which were purified by column chromatography using hexane−EtOAc as eluent.

1,5-Diphenyl-4-ethyl-3-(4′-methoxyphenyl)-1*H*-pyrazole (21l). Yield 65% (0.12 g); colorless solid; mp 121−122 °C (lit. 107−108 °C);[5] R_f 0.5 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3051, 2937, 1603, 1499, 1442, 1358, 1298 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.8 Hz, 2H), 7.32−7.34 (m, 3H), 7.14−7.26 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.62 (q, J = 7.3 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 150.6, 141.1, 140.1, 131.1, 130.1, 129.1, 128.6, 128.5, 128.2, 126.7, 126.5, 124.6, 120.6, 113.9, 55.3, 17.1, 15.5. MS (*m*/*z*, %): 355 (M + 1, 100), 354 (M^+, 60). Anal. Calcd for $C_{24}H_{22}N_2O$ (354.44): C, 81.43; H, 6.26; N, 7.90. Found: C, 81.52; H, 6.16; N, 7.98.

1,3-Diphenyl-4-ethyl-5-(4-methoxyphenyl)-1*H*-pyrazole (21m). Yield 61% (0.11 g); colorless solid; mp 110−111 °C (lit. yellow foam);[5] R_f 0.48 (9.2:0.8 hexanes−EtOAc). IR (KBr): 3066, 2964, 2931, 1611, 1554, 1502, 1453, 1360, 1289, 1249, 1176, 1105, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.1 Hz, 2H), 7.38 (t, J = 7.1 Hz, 1H), 7.24−7.30 (m, 5H), 7.15 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 3.81(s, 3H), 2.65 (q, J = 7.3 Hz, 2H), 1.03 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 150.8, 141.0, 140.2, 134.2, 131.3, 128.6, 128.4, 127.9, 127.5, 126.5, 124.6, 123.2, 120.2, 114.0, 55.2, 17.1, 15.6. MS (*m*/*z*, %): 355 (M + 1, 100), 354 (M^+, 60). Anal. Calcd for $C_{24}H_{22}N_2O$ (354.44): C, 81.43; H, 6.26; N, 7.90. Found: C, 81.52; H, 6.16; N, 7.98.

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Supporting Information Available: ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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