

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, ArNHNH₂/ t-BuOK/ t-BuOH/ Δ ; b, ArNHNH₂/ 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

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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 ketones⁶ or

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 β -dialkylamino/alkoxy/chloro ketones⁷ 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 aromatic11,13 and heteroaromatic^{11c,14} compounds in highly regiocontrolled fashion. In continuation of these studies, we now report regioselective synthesis of isomeric 1-aryl-3,4substituted-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-1} with phenyl and methylhydrazines yielding either

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

MeS	$ \begin{array}{c} R^{2} \\ \hline R^{2} \\ \hline SMe \end{array} \begin{array}{c} ArNHNH_{2} \\ \hline t-BuOK / t-BuOH \\ \Delta / 12 h \\ \hline Ar \\ \textbf{2, 7} \end{array} \begin{array}{c} R^{1} \\ \hline N \\ Ar \\ \textbf{2, 7} \end{array} $	<u>Raney-N</u> Me EtOH / 4-5 h		A^{R^2}
Entry	1, 2, 4, 7	Ar	%Yi 2	eld 4
1	1a, 2a, 4a, R ¹ = C ₆ H ₅ ; R ² = H	C_6H_5	98%	98%
2	1b , 2b , R ¹ = 4-CIC ₆ H ₄ ; R ² = H	C_6H_5	70%	-
3	1c, 2c, R ¹ = 4-MeOC ₆ H 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 ₆ H 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>i</i> -Pr; R ² = H	C_6H_5	71%	-
8	1h , 2h , R ¹ = CH(OMe) ₂ ; R ² = H	C_6H_5	а	
	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 ₆ H ₅ ; R ² = H	$4-FC_6H_4$	76%	-
13	1d, 7d , $R^1 = R^2 = C_6 H_5$	4-FC ₆ H ₄	80%	-
14	1 i, 7 i, $R^1 = R^2 =$	4-FC ₆ H ₄	88%	-

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

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.

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 reported¹⁶ 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 ·Et₂O 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 4k²¹ 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)-4,5substituted/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** (R¹ = C₆H₅, R² = 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 H₂S 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

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 TABLE 2. Synthesis of 1-Aryl-4,5-substituted/annulated

 3-(methylthio)pyrazoles

MeS S 9	$ \begin{array}{c} R^2 \\ \begin{array}{c} R^2 \\ R^1 \end{array} \xrightarrow{ArNHNH_2} \\ \hline R^1 \\ \hline EtOH/\Delta \\ 5 h \\ Ar \\ \hline 3, 11 \end{array} \end{array} \begin{array}{c} R^2 \\ N \\ Ar \\ \hline R^1 \\ Ar \\ \hline 3, 11 \end{array} $	Raney-N EtOH/	H N N Ar 10	R ² R ¹
Entry	2, 3, 9, 10, 11	Ar	%Yi 3	eld 10
1	9a, 3a, 10a, R ¹ = C ₆ H ₅ ; R ² = H	C_6H_5	81%	88%
2	9b , 3b , $R^1 = 4$ -CIC ₆ H ₄ ; $R^2 = H$	C_6H_5	68%	-
3	9c , 3c , R ¹ = 4-MeOC ₆ H 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 ₆ H 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>i</i> -Pr; R ² = H	C_6H_5	45%	-
8	9h, 2h, R ¹ = CH(OMe) ₂ ; R ² = H	C_6H_5	а	
	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	с	-
11	9k , R ¹ = R ² = −(CH ₂) ₄ −	C ₆ H ₅	d	е
12	9a, 11a, R ¹ = C ₆ H ₅ ; R ² = H	4-FC ₆ H ₄	69%	-
13	9d , 11d , $R^1 = R^2 = C_6 H_5$	4-FC ₆ H ₄	88%	-
14	9 i, 11 i, R ¹ = R ² =	4-FC ₆ H 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** ($\mathbf{R} = \mathbf{Me}$, 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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 a (a) m-CPBA (2.2 equiv)/DCM/0–rt/4 h; (b) $n\text{-}BuMgBr/NiCl_2\text{-}$ (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 crosscoupling²⁵ of the pyrazoles 2a and 3a with 4-methoxyphenyl Grignard reagent afforded the corresponding 1,3diphenyl-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-5methyl- 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 NiCl₂(PPh₃)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 **211,m**, which are shown to be high affinity binding and selective estrogen receptor (ER) ligands for ERa subtype (ERa).⁵ Thus the reaction of dithioesters **91,m** with phenylhydrazine afforded the corresponding 1,5-diaryl-4-ethyl-3-(methylthio)pyrazoles **201,m** in high yields. Subsequent nickel-catalyzed cross-coupling of **201,m** with either 4-methoxyphenyl or phenyl Grignard reagents, respectively, afforded the isomeric pyrazoles **211,m** in good yields (Scheme 3).

Conclusion

In summary, we have developed an efficient general synthesis of 1-aryl-3,4-substituted-5-(methylthio)-pyra-

SCHEME 3



zoles and 1-aryl-3-(methylthio)-4,5-subsituted pyrazoles from two regiospecific processes, namely, the cyclocondensation of arvlhydrazines 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 **211,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.

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-3,4substituted/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 CH₂Cl₂ (3 × 50 mL), washed with H₂O (2 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous Na₂SO₄. 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 (CH₂Cl₂): 3060, 2922, 1597, 1525, 1499, 1456, 1412, 1362, 1316 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 $\rm C_{16}H_{14}N_2S$ (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. ¹H NMR (400 MHz, CDCl₃): 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 = 8.5Hz, 2H), 1.92 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₁₇FN₂S (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 (CH₂Cl₂): 2962, 2925, 1596, 1507, 1458, 1424, 1371 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₆N₂S (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 H₂O (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na₂SO₄. 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. ¹H NMR (400 MHz, CDCl₃): δ 7.20–7.26 (m, 8H), 7.15–7.18 (m, 2H), 6.39 (s, 1H), 2.55 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₁₄N₂S (2666.37): 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₁₇FN₂S (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 (CH₂Cl₂): 2966, 2927, 1595, 1527, 1500, 1453, 1358 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₆N₂S (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 Et₂O was added dropwise to a stirring suspension of $(\rm Ph_3P)_2NiCl_2$ (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 \times 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)-1H-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 (CH₂Cl₂): 3052, 2929, 1612, 1519, 1495, 1458, 1361, 1293, 1250 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₁₈N₂O (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)-1H-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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₁₈N₂O (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 CH₂Cl₂ (3 × 50 mL), washed with H₂O (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na₂SO₄. 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 (201).** 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₁₈N₂S (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-1H-pyrazole (20m). Yield 72% (1.17 g); red viscous liquid; R_f 0.47 (9.2:0.8 hexanes—EtOAc). IR (CH₂Cl₂): 2963, 2927, 1612, 1597, 1575, 1505, 1459, 1433, 1391, 1353, 1289, 1176 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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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 $\rm C_{19}H_{20}N_2OS~(324.44):\ C,~70.34;$ 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 211,m. A solution of respective Grignard reagent (0.05 mmol) in Et₂O was added dropwise to a stirring suspension of NiCl₂(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-MeOC₆H₄MgBr) and a solution of pyrazoles 201 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 NH₄Cl solution, and extracted with CH₂Cl₂ (3 × 25 mL). The organic layer was dried (anhydrous Na₂SO₄) and evaporated to give crude products 211 or 21m, which were purified by column chromatography using hexane–EtOAc as eluent.

1,5-Diphenyl-4-ethyl-3-(4'-methoxyphenyl)-1H-pyrazole (211). 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, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₄H₂₂N₂O (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, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): δ 1595, 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 C₂₄H₂₂N₂O (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 ¹³C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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