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Cyclocondensation of Arylhydrazines with 1,3-Bis(het)arylmonothio-1,3-diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-Aryl-3,5-bis(het)arylpyrazoles with Complementary Regioselectivity

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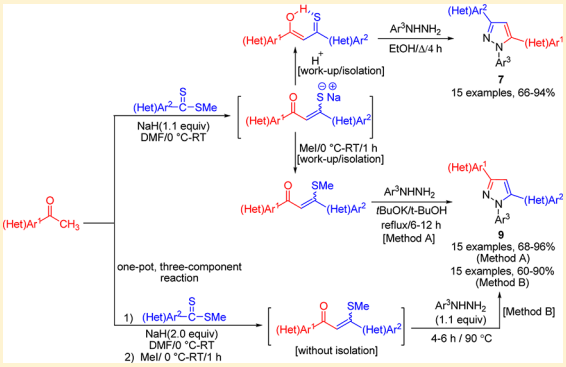
Supporting Information

ABSTRACT: Two efficient highly regioselective routes for the synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles with complementary regioselectivity starting from active methylene ketones have been reported. In the first protocol, the newly synthesized 1,3-bis(het)aryl-monothio-1,3-diketone precursors (prepared by condensation of active methylene ketones with het(aryl) dithioesters in the presence of sodium hydride) were reacted with arylhydrazines in refluxing ethanol under neutral conditions, furnishing 1-aryl-3,5-bis(het)-arylpyrazoles **7**, in which the het(aryl) moiety attached to the thiocarbonyl group of monothio-1,3-diketones is installed at the 3-position. In the second method, the corresponding 3-(methylthio)-1,3-bis(het)aryl-2-propenones (prepared in situ by base-induced alkylation of 1,3-monothiodiketones) were condensed with arylhydrazines in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, yielding 1-aryl-3,5-bis(het)arylpyrazoles **9** with complementary regioselectivity (method A). The efficiency of this protocol was further improved by developing a one-pot, three-component procedure for the synthesis of pyrazoles **9**, directly from active methylene ketones, by reacting in situ generated 3-(methylthio)-1,3-bis(het)aryl-2-propenones with arylhydrazines in the presence of sodium hydride (instead of potassium *tert*-butoxide as base). The structures and regiochemistry of newly synthesized pyrazoles were confirmed from their spectral and analytical data along with X-ray crystallographic data of three pairs of regioisomers.



INTRODUCTION

Substituted pyrazoles, though rarely found in nature, serve as important synthetic targets in medicinal chemistry and the pharmaceutical industry.[1] Both 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles constitute the core structure of several commercial drugs such as Celebrex,[2] Viagra,[3] Acomplia, and the insecticide Fipronil as well as numerous other compounds that exhibit a wide spectrum of biological activities such as anti-inflammatory, analgesic, sedative, and hypnotic properties and ligands for estrogen receptors.[4] Many of the substituted pyrazoles are useful in crop protection[5] as herbicides[6] and pesticides.[7] Furthermore, substituted pyrazoles are also used as ligands in coordination chemistry[8] as well as optical brighteners,[9] as UV stabilizers,[10] as photoelectron-induced electron transfer systems,[11] and as supramolecular entity units.[12] As a result, there is continuing interest in the development of efficient and versatile methods to access highly substituted pyrazoles.[1,13]

One of the most popular, oldest, and frequently used methods for the synthesis of 1,3,5-trisubstituted pyrazoles is classical cyclocondensation of monosubstituted hydrazines with 1,3-dicarbonyl compounds (Knorr synthesis) or surrogates thereof.[14] However, the appealing generality of this method is somewhat vitiated due to the frequent formation of a regioisomeric mixture of unsymmetrical pyrazoles in these reactions.[4c,d,15] Modification of this method by employing α,β-acetylenic or olefinic ketones instead of 1,3-diketones usually allow better control of regioselectivity.[15e,16] However, in the synthesis of 1-substituted 3,5-diarylpyrazoles, in which 3- and 5-aryl groups are similarly substituted, with only minor differences in the electronic and steric nature of substituents, the complete control of regioselectivity becomes a daunting task. The other important method for the synthesis of substituted pyrazoles,

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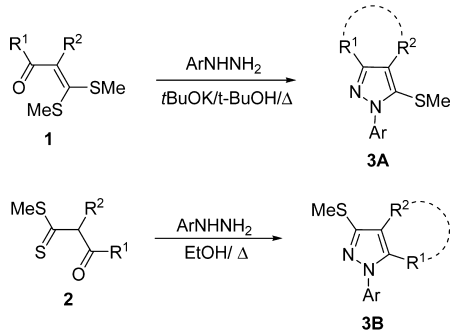
involving 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins and alkynes,[13b,17] has found only limited applications, because these 1,3-dipoles are often difficult to prepare and potentially explosive.[17] Although recent efforts have greatly expanded the generality of these de novo approaches, each method has its scope and efficiency limitations.[13−15,18] Since subtle variations and combinations of arylation patterns on the pyrazole motif have profound effects on the biological activity,[2c,4e] the development of efficient and general protocols for regiocontrolled synthesis of polysubstituted pyrazoles is highly desirable.

We have earlier reported a regioselective synthesis of 1-aryl-3,4-(or 4,5-)substituted 5-(or 3-)(methylthio)pyrazoles **3A**,**B** by cyclocondensation of arylhydrazines with either α-oxoketene dithioacetals **1** or β-oxodithioesters **2**, respectively (Scheme 1).[19a]

Scheme 1. Regioselective Synthesis of 4,5-Substituted 5-(or 3-)(methylthio)pyrazoles[19a]



The 5-(or 3-)methylthio functionality in these isomeric pyrazoles could be further elaborated for regiocontrolled introduction of 5-(or 3-)aryl/alkyl groups by nickel-catalyzed cross-coupling with the appropriate Grignard reagents. We have also utilized these regioisomeric pyrazoles for the synthesis of novel tetrasubstituted 3-(or 5-)(methylthio)-1,4,5-tri(het)aryl and -1,3,4-tri(het)-arylpyrazoles by introduction of a (hetero)aryl group at their C-4 position through halogenation followed by Suzuki cross-coupling with a series of (het)aryl boronic acids.[19c] During the course of these studies along with our continued interest in the design and development of new organosulfur synthons as precursors for diversity-oriented synthesis of novel heterocycles,[20] we became interested in monothio-1,3-diketones of the general structure **6** as potentially useful 3-carbon 1,3-bielectrophilic synthons for regiospecific construction of five- and six-membered heterocycles. Since, in Knorr pyrazole synthesis, the regioselectivity of the reaction relies on differential reactivities of two carbonyl groups of 1,3-diketones, it was anticipated that cyclocondensation of monothio-1,3-diketones with various unsymmetrical hetero-binucleophiles (i.e., monosubstituted hydrazines, hydroxylamine, etc.) would be intrinsically more regioselective, because of the significant difference in reactivity and electronic properties of carbonyl and thiocarbonyl groups. Our literature survey at this stage revealed that monothio-1,3-diketones and the corresponding β-thioxoesters have been known for a long time[21] and these intermediates have attracted considerable attention in the past as chelating agents, with promising applications, especially in analytical chemistry.[21,22] However, the synthetic potential of these compounds as useful precursors for regiospecific synthesis of five- and six-membered heterocycles is virtually unexplored.[23]

We describe herein a highly regioselective route for the synthesis of 1-aryl-3,5-bis(het)arylpyrazoles **7** via cyclocondensation of arylhydrazines with various monothio-1,3-diketones (Table 1). Further, we have also developed an efficient synthesis of 1-aryl-3,5-bis(het)arylpyrazoles **9** with complementary regioselectivity by base-mediated reactions of arylhydrazines with 1,3-bis(het)aryl-3-(methylthio)-2-propenones **8** (prepared in situ by S-methylation of 1,3-monothiodiketones **6**) (Table 2) or directly from active methylene ketones **4** in a one-pot, three-component reaction (Scheme 4, Table 2). The results of these studies are reported in this paper.

Scheme 2. Synthesis of 1,3-Bis[(het)aryl]-1,3-monothiodiketones 6a−m, 3-(Methylthio)-β-(het)aryl-2-propenones 8a−m, and the Corresponding Cyclic Analogues 6n,o and 8n,o

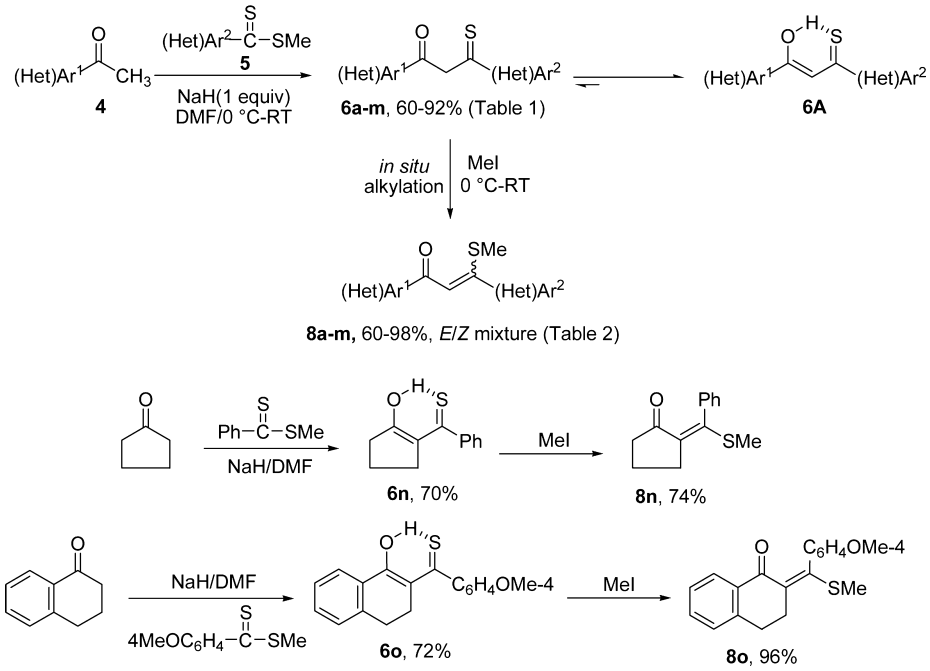
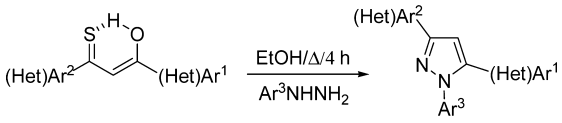


Table 1. Regioselective Synthesis of 1-Aryl-3,5-bis(het)aryl/annulated Pyrazoles 7a−m and 7n−o from 1,3-Monothio-β-diketones 6[a]

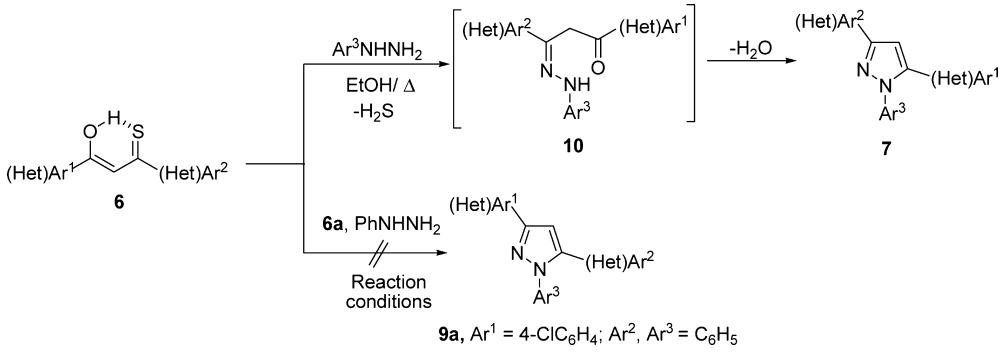


6a-o **7a-o**

Entry[a]	6	% Yield 6	Ar3	7	%Yield 7
1	**6a**, R_1=H, R_2=4-Cl	84%	C_6H_5	**7a**, R_1,R_3=H, R_2=4-Cl	92%
2	**6b**, R_1=OMe, R_2=3-Br	79%	C_6H_5	**7b**, R_1=OMe, R_2=3-Br, R_3=H	86%
3	**6c**, R_1=H, R_2=4-MeO	80%	4-ClC_6H_4	**7c**, R_1=H, R_2=4-MeO, R_3=4-Cl	86%
4	**6d**, R_1=H	86%	C_6H_5	**7d**, R_1=R_2=H	87%
5	**6e**, R_1=MeO	60%	4-BrC_6H_4	**7e**, R_1=MeO, R_2=Br	73%
6	**6f**	67%	4-$MeOC_6H_4$	**7f**	79%
7	**6g**	66%	C_6H_5	**7g**	77%
8	**6h**	84%	4-$MeOC_6H_4$	**7h**	79%
9	**6i**	86%	4-$MeOC_6H_4$	**7i**	92%
10	**6j**	78%	4-$MeOC_6H_4$	**7j**	90%
11	**6k**	90%	4-ClC_6H_4	**7k**	96%
12	**6l**	92%	C_6H_5	**7l**	84%
13	**6m**	60%	4-FC_6H_4	**7m**	81%
14	**6n**	70%	C_6H_5	**7n**	68%
15	**6o**	72%	C_6H_5	**7o**	85%

[a]Reaction conditions: **6** (5.0 mmol), arylhydrazine (5.5 mmol), in EtOH, reflux, 4 h.

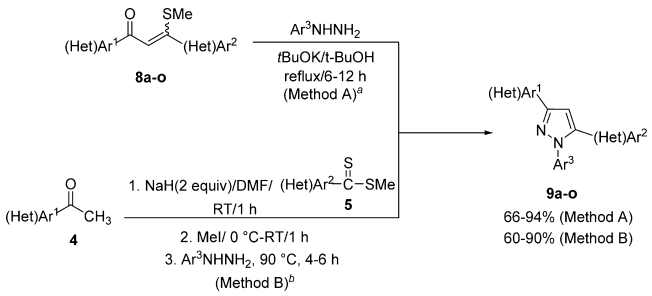
Scheme 3. Regioselective Synthesis of 1-Aryl-3,5-bis(het)arylpyrazoles 7 from 1,3-Monothiodiketones 6 and Attempted Synthesis of Regioisomeric Pyrazoles 9 from 6



RESULTS AND DISCUSSION

The desired 1,3-substituted monothio-1,3-diketones **6a−m** and the corresponding cyclic derivatives **6n−o** were prepared in excellent yields *via* modification of the reported procedure[24] by base induced thioacylation of various (het)aryl methyl ketones **4** (or cyclic ketones) with dithioesters **5** in the presence of sodium hydride in DMF (Scheme 2). The structures of all these newly synthesized monothio-1,3-diketones were established with the

Table 2. Synthesis of Regioisomeric 1-Aryl-3,5-bis(het)aryl/annulated Pyrazoles 9a–m and 9n–o from 3-(Methylthio)propenones 8 (Method A)[a] and via a One-Pot, Three-Component Reaction (Method B)[b]



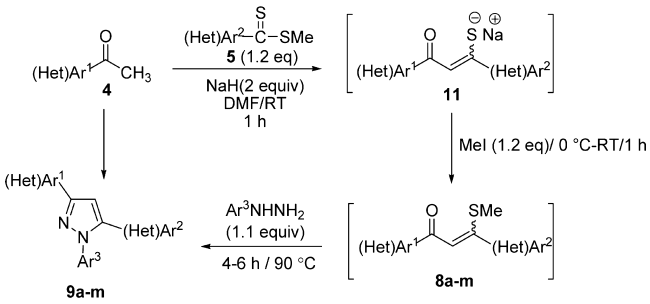
Entry	8	% Yield 8	Ar3	9	%Yield 9c Method A (Method B)
1	**8a**, R_1=H, R_2=4-Cl	98%	C_6H_5	**9a**, R_1=R_3=H, R_2=4-Cl	87% (85%)
2	**8b**, R_1=OMe, R_2=3-Br	67%	C_6H_5	**9b**, R_1=OMe, R_2=3-Br, R_3=H	72% (70%)
3	**8c**, R_1=H, R_2=4-OMe	95%	4-ClC_6H_4	**9c**, R_1=H, R_2=4-MeO, R_3=Cl	82% (80%)
4	**8d**, R_1=H	72%	C_6H_5	**9d**, R_1=R_2=H	82% (80%)
5	**8e**, R_1=OMe	71%	4-BrC_6H_4	**9e**, R_1=OMe, R_2=Br	83% (78%)
6	**8f**	75%	4-$MeOC_6H_4$	**9f**	94% (90%)
7	**8g**	78%	C_6H_4	**9g**	83% (80%)
8	**8h**	60%	4-$MeOC_6H_4$	**9h**	93% (90%)
9	**8i**	96%	C_6H_5	**9i**	90% (85%)
10	**8j**	92%	4-ClC_6H_4	**9j**	86% (85%)
11	**8k**	96%	4-ClC_6H_4	**9k**	94% (90%)
12	**8l**	90%	C_6H_5	**9l**	78% (80%)
13	**8m**	86%	4-FC_6H_4	**9m**	84% (78%)
14	**8n**	74%	C_6H_5	**9n**	66% (60%)
15	**8o**	96%	C_6H_5	**9o**	82% (78%)

[a]Method A, reaction conditions: **8** (5.0 mmol), arylhydrazine (5.5 mmol), *t*-BuOK (5.5 mmol) in *t*-BuOH, reflux, 6–12 h. [b]Method B, reaction conditions: ketone **4** (1.0 mmol), dithioester **5** (1.2 mmol), NaH (2.0 mmol, 100%), MeI (1.2 mmol), Ar^3NHNH_2 (1.1 mmol), in DMF, 90 °C, 4–6 h. [c]Yields in parantheses are yields of **9** by method B.

help of ^{1}H and ^{13}C spectral and analytical data. The ^{1}H NMR spectra of **6** show that all these monothiodiketones exist in the thioenol tautomeric form **6A**, as is evident from the presence of a low-field signal at δ 16.2–12.02 due to the enolic OH group, as reported earlier.[23c,24b,25] The corresponding 3-(methylthio)-3-(het)aryl-2-propenone precursors **8a–m**[23c,26,27] were obtained in good yields by in situ S-methylation of thioenolates of monothiodiketones **6** generated in the presence of sodium hydride as base (Scheme 2). These β-(methylthio)propenones **8** are found to be mixtures of *E*/*Z* stereoisomers from their ^{1}H NMR spectra.

The reaction of unsymmetrically substituted 1,3-monothio-β-diketone **6a** with phenylhydrazine was first examined under varying conditions and solvents with a view to optimize the reaction conditions for regioselective synthesis of 1,3,5-triarylpyrazole **7a** (Table 1). Our studies revealed that the reaction of **6a** and phenylhydrazine was very clean under neutral conditions in the presence of protic solvents (EtOH, MeOH, *t*-BuOH), yielding only one product, whereas under mildly acidic or basic conditions, intractable mixtures of several products were formed. The best results were obtained when equimolar quantities of **6a** and phenylhydrazine were refluxed in ethanol for 4 h, furnishing only one product, which was characterized as 1,3-diphenyl-5-(4-chlorophenyl)pyrazole (**7a**; 92%) on the basis of its spectral and analytical data (Scheme 3; Table 1, entry 1) and by comparison with the reported data.[16b,23c,28] Further, the regiochemistry of triarylpyrazole **7a** was unambiguously established by its X-ray crystal structure analysis (Figure S1, Supporting Information). Similarly, the unsymmetrically substituted 1-phenyl-3-(4-methoxyphenyl)-5-(3-bromophenyl)pyrazole (**7b**) was also isolated in excellent yield as a single regioisomer by reacting monothiodiketone **6b** with phenylhydrazine under identical conditions (Table 1, entry 2). The regioselectivity of the reaction was further demonstrated by employing a substituted phenylhydrazine such

Scheme 4. Synthesis of Regioisomeric 1-Aryl-3,5-bis(het)arylpyrazoles via a One-Pot, Three-Component Reaction (Method B)



as 4-chlorophenylhydrazine as a coupling partner with the monothio-1,3-diketone **6c**, providing the corresponding 1-(4-chlorophenyl)-3-phenyl-5-(4-methoxyphenyl)pyrazole **7c** in 86% yield (Table 1, entry 3). The substrate scope and the regioselectivity of the reaction were further established by subjecting a number of heteroaryl-substituted monothio-β-diketones to cyclocondensation with various arylhydrazines, and the results are depicted in Table 1 (entries 4−12). Thus, the reaction of 3-(4-pyridyl)-1-phenyl monothiodiketone **6d** with phenylhydrazine afforded the corresponding 1,3-diphenyl-5-(4-pyridyl)pyrazole (**7d**) exclusively in 87% yield (entry 4). The regiochemistry of substituents in **7d** was independently confirmed by an X-ray crystal structure (Figure S2, Supporting Information). Similarly a range of (hetero)aryl substituted pyrazoles with 4-pyridyl (**7e**), 2-thienyl (**7f,g**), and 2-(*N*-methylpyrrolyl) (**7h**) moieties could be synthesized in high yields by reacting the appropriate monothiodiketones **6e−h** with representative arylhydrazines (entries 5−8). It is noteworthy that sterically demanding substituents could also be well tolerated in the pyrazoles **7f−g** without affecting the regiochemistry of reaction (entries 6 and 7).

The versatility and substrate scope of the reaction was further elaborated by installation of two heteroaryl groups in the product pyrazoles **7** in a highly regiocontrolled fashion (Table 1, entries 9−12). Thus, the 1-*N*-phenylpyrazole **7i** bearing biologically important 3-(3-indolyl) and 5-(3-pyridyl) groups was obtained as the exclusive product in 92% yield from the corresponding monothio-β-diketone **6i** and phenylhydrazine under the optimized reaction conditions (entry 9). The structure of **7i** was unequivocally confirmed from its X-ray crystal structure (Figure S3, Supporting Information). Similarly the other regiospecifically substituted 1-*N*-aryl-3,5-bis(het)arylpyrazoles **7j−l** with diverse combinations of 2-furyl/2-thienyl/3-indolyl/3-pyridyl groups at the 3- and 5-positions were readily obtained in excellent yields by this novel and simple protocol (Table 1, entries 10−12). The reaction was found to be compatible with aliphatic monothio-1,3-diketone **6m** also, and a methyl group could be successfully placed at the 3-position of the pyrazole **7m** by reaction with 4-fluorophenylhydrazine (Table 1, entry 13).

We next explored the reaction of cyclic monothio-1,3-diketones such as **6n,o** with a view to broaden further scope of the reaction for the regiospecific synthesis of annulated pyrazoles (entries 14 and 15). To our delight, refluxing a mixture of either **6n** or **6o** and phenylhydrazine in ethanol provided the corresponding 4,5-(cyclopenta)pyrazole **7n** and dihydrobenzoindazole derivative **7o** in good yields and only a single regioisomer could be identified from the reaction mixture.

Although no attempts were made to study the detailed mechanism of this novel, highly regioselective synthesis of unsymmetrically substituted 1,3,5-tri(het)arylpyrazoles **7** from 1,3-di(het)-arylmonothio-β-diketones **6**, it is apparent from the structure of product pyrazoles **7** that the reaction proceeds by nucleophilic addition of the NH_2 group of phenylhydrazine to the thiocarbonyl group of **6** with concomitant elimination of H_2S to give the intermediate ketohydrazone **10**, which on subsequent dehydrative cyclization affords the pyrazoles **7** as exclusive products (Scheme 3). However, our attempts to isolate the phenyl hydrazone **10** under various reaction conditions were not successful.

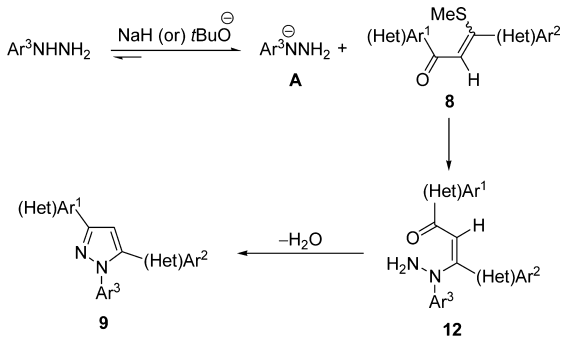
After successfully accomplishing the regiospecific synthesis of 1,3,5-triarylpyrazoles **7** from monothio-β-diketones **6**, in which the (het)aryl substituent attached to the thiocarbonyl group of monothioketone **6** is installed at the 3-position of the product pyrazoles **7**, we were further intrigued by the idea of reversing the reactivity of **6** toward arylhydrazines by varying the reaction conditions, so as to develop a general synthesis of regioisomeric pyrazoles **9** in which the (het)aryl substituent attached to the carbonyl group of **6** occupies the 3-position of product pyrazoles (Scheme 3). However, our various attempts to procure the pyrazole **9a** by reacting **6a** with phenylhydrazine under neutral, mildly acidic, or mildly basic conditions led only to frustrating results, yielding only intractable reaction mixtures. On the other hand, in a parallel study, we focused our attention toward β-(methylthio)-β-(het)arylenones **8**, which were readily available in a one-pot reaction by direct in situ S-methylation of the product 1,3-monothioketones **6** prepared by base-induced condensation of aryl methyl ketones with dithioesters (Scheme 2).[23b,24d,26,29,30] As a model experiment, we therefore investigated the reaction of unsymmetrical 1,3-bis(het)aryl-3-(methylthio)-2-propenone **8a** with phenylhydrazine under a variety of reaction conditions (neutral, acidic, basic) with a view to obtain the regioisomeric 1,3,5-tri(het)arylpyrazole **9a** (Table 2). To our delight, when **8a** was reacted with phenylhydrazine in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol under our earlier described conditions,[19a,31] workup and analysis of the reaction mixture revealed the formation of only one product, which was identified as the desired regioisomeric 1,5-diphenyl-3-(4-chlorophenyl) pyrazole **9a** from its spectral and analytical data and by comparison with the reported data (Table 2, entry 1).[16b,32] The structure and regiochemistry of **9a** was further confirmed independently by its X-ray crystal analysis (Figure S4, Supporting Information). The generality of the reaction was established by the synthesis of other regioisomeric 1-aryl-3,5-bis(het)arylpyrazoles **9b−n** with complete regioselectivity by cyclocondensation of the appropriate 1,3-bis(hetero)-aryl-3-(methylthio)-2-propenones **8b−l** with various arylhydrazines under identical conditions (Table 2, entries 2−12). The corresponding 5-methyl-3-(4-methoxyphenyl)pyrazole **9m** was also obtained in good yield from the respective β-methyl-substituted enone **8m** (Table 2, entry 13). Similarly, the cyclic β-[(methylthio)arylidene] ketones **8n,o** were smoothly transformed into the corresponding regioisomeric condensed pyrazoles **9n,o** when they were reacted with phenylhydrazine under the optimized reaction conditions (Table 2, entries 14 and 15). The structures of all these newly synthesized regioisomeric pyrazoles **9a−o** were established with the help of spectral and analytical data. Further structural proof for regiochemistry was unambiguously provided by the X-ray crystal structures of pyrazoles **9d,i**, which were found to be regioisomeric with the pyrazoles **7d,i**, respectively with exchange of substituents at 3- and 5-positions (Figures S5 and S6, Supporting Information).

Having established the synthesis of both regioisomeric 1,3,5-trisubstituted pyrazoles **7** and **9** from 1,3-monothiodiketone and

1,3-bis(het)aryl-3-(methylthio)-2-propenone precursors **6** and **8**, respectively, we became interested in developing a one-pot, three-component synthesis of the trisubstituted pyrazoles **9** directly from active methylene ketones and dithioesters **5** without isolation of β-(methylthio)enone intermediates **8** (Scheme 4). Thus in a model experiment, when 4-chloroacetophenone was reacted with dithioester **5a** ($Ar^2 = C_6H_5$) in the presence of NaH (2 equiv) in DMF at room temperature followed by sequential addition of methyl iodide and phenylhydrazine (monitored by TLC) and subsequent heating at 90 °C (4−6 h) (method B), workup of the reaction mixture yielded 1,5-diphenyl-3-(4-chlorophenyl)pyrazole (**9a**) exclusively in a yield (85%) comparable to that of method A (Table 2, entry 1) and no trace of the isomeric pyrazole **7a** was detected in the reaction mixture.These reaction conditions were found to be applicable to all active methylene ketones **4**, and the corresponding pyrazoles **9b−o** were obtained as exclusive products in 60−90% overall yields (Table 2, entries 2−15, method B) comparable to those from reaction of pure β-(methylthio)enones **8** and arylhydrazines in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol (method A, Table 2).

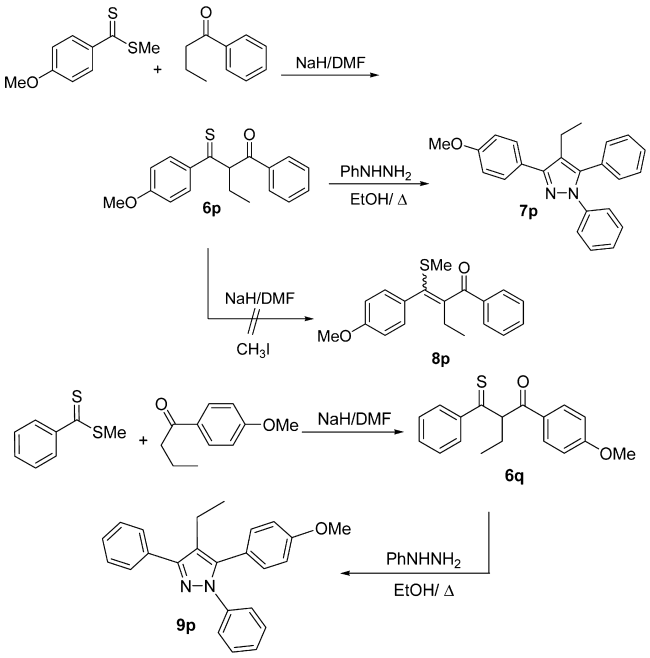
The probable mechanism for the regioselective formation of the pyrazoles **9** from the reaction of arylhydrazines with 1,3-bis(het)arylpropen-2-ones **8** in the presences of bases such as potassium *tert*-butoxide and NaH appears to be similar to that suggested by us for the base-mediated formation of 1,3-diaryl-5-(cycloamino)pyrazoles from the corresponding N,S-acetals in our previous study.[19b] Thus, the anion **A**, generated by abstraction of the more acidic proton of arylhydrazine with base, undergoes conjugate addition−elimination with 3-(methylthio)-propenones **8** followed by intramolecular cyclization of the resulting intermediate **12**, yielding pyrazoles **9** as the exclusive products (Scheme 5).

Scheme 5. Probable Mechanism for the Formation of 1-Aryl-3,5-bis(het)arylpyrazoles 9 from 1,3-Substituted Propen-2-ones 8



We further contemplated to expand the scope of the reaction for the synthesis of 1,3,4,5-tetrasubstituted pyrazoles such as **7p** and **9p**, which have been shown to be high-affinity binding and selective estrogen receptor (ER) ligands for the ERα subtype.[19a,33] Thus, the desired precursor α-ethyl-(4-methoxyphenyl)-1,3-monothioketone **6p** was prepared by condensation of butyrophenone with 4-(methoxyphenyl) dithioester under conditions described earlier (Scheme 6). The monothiodiketone **6p** was found to be unstable and was reacted with phenylhydrazine without further purification in refluxing ethanol, furnishing the tetrasubstituted 1,3,5-triaryl-4-ethylpyrazole **7p** in 75% yield (Scheme 6). However attempted in situ S-alkylation of monothiodiketone **6p** with methyl iodide under conditions

Scheme 6. Regioselective Synthesis of 1,3,4,5-Tetrasubstituted Pyrazoles 7p and 9p as Selective Estrogen Receptors



discussed earlier failed to give tetrasubstituted β-methylthioenone **8p**, which was required for the synthesis of regioisomeric pyrazole **9p** (Scheme 6). We therefore synthesized the pyrazole **9p** via an alternate route by reacting isomeric monothiodiketone **6q** (prepared from phenyldithioester and 4-methoxybutyrophenone) with phenylhydrazine under conditions described earlier, as shown in Scheme 6. The structures of pyrazoles **7p** and **9p** were established by comparison of their physical and spectral data with those of the reported compounds.[19a]

■ CONCLUSION

In summary, we have developed an efficient general synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles via two highly regioselective processes: namely the cyclocondensation of arylhydrazines with either 1,3-bis(het)aryl monothio-β-diketones **6** or 1,3-bis(het)aryl-3-(methylthio)-2-propenones **8**. These two protocols are complementary to each other in terms of regioselectivity of substituents at the 3- and 5-positions of pyrazoles **7** and **9**. The flexibility and generality of this newly developed protocol has been demonstrated by the efficient and regiocontrolled preparation of a range of 1-aryl-3,5-bis(het)aryl pyrazoles with minor differences in the electronic/steric character of 3- and 5-(hetero)aryl substituents. The efficiency of this protocol has been further improved by developing a one-pot, three-component reaction for the synthesis of pyrazole **9** directly from active methylene ketones **4** without isolation of β-(methylthio)propenone precursors **8** (Scheme 4, method B). It should be noted that Yu and co-workers have synthesized β-(ethylthio)-1,3-substituted propenone precursors such as **8** by Liebeskind−Srogl cross-coupling, requiring prior synthesis of α-oxoketene dithioacetals from active methylene ketones.[26g,h] The ready availability of starting materials along with mild and simple reaction conditions allowing rapid assembly of a diversely substituted pyrazole core in a highly regiocontrolled manner should make these reactions suitable for combinatorial synthesis in drug discovery research. We anticipate that our approach along

with other reported de novo synthesis of pyrazoles will find application in both academia and particularly in industry. Further, it should be noted that the synthetic applications of 1,3-monothiodiketones, unlike their 1,3-diketone counterparts, is virtually unexplored, especially for the regioselective synthesis of five- and six-membered heterocycles. Further work in this direction is in progress and will be published in due course.

■ EXPERIMENTAL SECTION

General Information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin-layer chromatography using Merck TLC silica gel plates and visualized with UV light. Column chromatography was performed using Merck silica gel (100−200 mesh). Nuclear magnetic resonance spectra were recorded on a (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$ as solvent. Chemical shifts are reported in δ ppm (parts per million) using residual solvent protons as the internal standard (δ 7.26 for $CDCl_3$ in ^{1}H NMR, δ 77.16 for $CDCl_3$ in ^{13}C NMR). Coupling constants are reported as J values in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), ddd, (doublet of doublet of doublet), quin (quintet), m (multiplet), and br (broad). Infrared spectra were recorded using an FTIR instrument and HRMS on a Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. X-ray single crystal data of all six crystals was collected on a diffractometer using Mo Kα radiation (λ = 0.71073 Å) at room temperature. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least squares against F^2 using SHELXL-97 software. All the active methylene ketones **4a**−**k** were commercially purchased, and the corresponding dithioesters **5a**−**e**,[34] **5h**,[34] and **5f**,**g**[20f] were prepared according to the reported methods in the literature.

General Procedure for the Preparation of 1,3-Monothio-β-diketones (1-(Het)aryl-3-thioxo-3-alkyl/(hetero)aryl propan-1-one) 6. To a stirred suspension of NaH (1.1 mmol, 100%) in DMF (20 mL) under an N_2 atmosphere was added dropwise a solution of (het)aryl methyl ketone **4** (1.0 mmol) and (het)aryl dithioester **5** (1.2 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 1 h (monitored by TLC) and was poured into ice-cold water (100 mL) and acidified with acetic acid. The aqueous layer was extracted with EtOAc (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude monothiodiketones **6**, which were purified by column chromatography using hexane/EtOAc as eluent.

The monothiodiketones **6p**,**q** were found to be unstable and decomposed during purification by colum chromatography. Therefore, the ketones **6p**,**q** could not be characterized and used as such for the preparation of pyrazoles **7p** and **9p** without purification.

*(Z)-3-(4-Chlorophenyl)-3-hydroxy-1-phenylprop-2-ene-1-thione (**6a**):* obtained from 4-chloroacetophenone (**4a**) and dithioester **5a** (Ar = C_6H_5), red solid (0.24 g, 84%); mp 112−113 °C; R_f = 0.7 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1583, 1549, 1482, 1246, 1087, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.91 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.81−7.78 (m, 2H), 7.52−7.42 (m, 5H), 7.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 178.5, 145.2, 138.8, 134.2, 131.2, 129.2, 128.6, 128.5, 126.8, 110.4; HRMS (ESI) m/z calcd for $C_{15}H_{11}ClOS$ [M + H]$^+$ 275.0297, found 275.0283.

*(Z)-3-(3-Bromophenyl)-3-hydroxy-1-(4-methoxyphenyl)prop-2-ene-1-thione (**6b**):* obtained from 3-bromoacetophenone (**4b**) and dithioester **5b** (Ar = 4-MeOC_6H_4), red viscous liquid (0.28 g, 79%); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1727, 1447, 1258, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.61 (s, 1H), 8.11 (t, J = 1.6 Hz, 1H), 7.92−7.90 (m, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.68−7.65 (m, 1H), 7.38−7.34 (m, 2H), 6.94 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 176.5, 163.0, 138.2, 138.1, 135.1, 130.5, 130.1, 129.1, 125.7, 123.2, 114.0, 108.8, 55.7; HRMS (ESI) m/z calcd for $C_{16}H_{13}BrO_2S$ [M + H]$^+$ 348.9898, found 348.9885.

*(Z)-3-Hydroxy-3-(4-methoxyphenyl)-1-phenylprop-2-ene-1-thione (**6c**):* obtained from 4-methoxyacetophenone (**4c**) and dithioester **5a**, red solid (0.22 g, 80%); mp 121−122 °C; R_f = 0.7 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2927, 1603, 1549, 1501, 1231, 1176, 817; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.95 (s, 1H), 8.0−7.9 (m, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.58−7.54 (m, 1H), 7.51−7.47 (m, 2H), 7.44 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 179.4, 163.5, 145.6, 130.8, 129.4, 128.4, 127.7, 126.8, 114.2, 110.1, 55.5; HRMS (ESI) m/z calcd for $C_{16}H_{14}O_2S$ [M + H]$^+$ 271.0793, found 271.0780.

*(Z)-3-Hydroxy-1-phenyl-3-(pyridin-4-yl)prop-2-ene-1-thione (**6d**)::* obtained from 4-acetylpyridine (**4d**) and dithioester **5a**, red viscous liquid (0.71g, 86%); R_f = 0.4 (3/2 EtOAc/hexane); IR (KBr, cm^{-1}) 3027, 2918, 1641, 1541, 1236, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.75 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 5.2 Hz, 2H), 7.46−7.44 (m, 3H), 7.31−7.25 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 167.3, 148.2, 138.0, 133.9, 128.8, 128.4, 127.6, 123.6, 107.8; HRMS (ESI) m/z calcd for $C_{14}H_{11}NOS$ [M]$^+$ 241.0561, found 241.0549.

*(Z)-1-(3,4-Dimethoxyphenyl)-3-hydroxy-3-(pyridin-4-yl)prop-2-ene-1-thione (**6e**):* obtained from 4-acetylpyridine (**4d**) and dithioester **5c** (Ar = 3,4-$(MeO)_2C_6H_3$), red viscous liquid (0.75 g, 60%): R_f = 0.35 (3/2 EtOAc/hexane); IR (KBr, cm^{-1}) 2933, 1575, 1512, 1267, 1141, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.74 (s, 1H), 8.79 (dd, J = 4.8 Hz, 1.6 Hz, 2H), 7.79 (dd, J = 4.8 Hz, 1.6 Hz, 2H), 7.53 (td, J = 8.4 Hz, 2.4 Hz, 2H), 7.42 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 174.0, 153.2, 150.9, 149.2, 143.2, 138.6, 120.3, 120.0, 111.1, 110.4, 108.6, 56.3, 56.2; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO_3S$ [M + H]$^+$ 302.0851, found 302.0847.

*(Z)-3-(2,5-Dimethylphenyl)-3-hydroxy-1-(thiophen-2-yl)prop-2-ene-1-thione (**6f**):* obtained from 2,5-dimethylacetophenone (**4e**) and dithioester **5e** ((Het)aryl = 2-thienyl) red liquid (0.18 g, 67%); R_f = 0.7 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1549, 1406, 1246, 807; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.02 (s, 1H), 7.72 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.62 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.34 (s, 1H), 7.22−7.16 (m, 2H), 7.12 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 7.06 (s, 1H), 2.50 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 180.4, 152.4, 135.8, 135.7, 134.4, 134.0, 131.7, 131.5, 129.0, 128.8, 127.7, 110.9, 21.0, 20.4; HRMS (ESI) m/z calcd for $C_{15}H_{14}OS_2$ [M + H]$^+$ 275.0564, found 275.0560.

*(Z)-3-Hydroxy-3-(3-methylthiophen-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-ene-1-thione (**6g**):* obtained from 2-acetyl-3-methylthiophene (**4f**) and dithioester **5d** (Ar = 3,4,5-$(MeO)_3C_6H_2$), red solid (0.23 g, 66%); mp 55−56 °C; R_f = 0.6 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2931, 1557, 1500, 1320, 1239, 1128, 801; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.28 (s, 1H), 7.68 (d, J = 5.4 Hz, 1H), 7.17 (s, 1H), 7.01 (s, 2H), 6.85 (d, J = 5.4 Hz, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 175.4, 153.1, 149.4, 140.3, 131.6, 131.4, 127.5, 110.4, 104.7, 104.6, 61.2, 56.6, 16.3; HRMS (ESI) m/z calcd for $C_{17}H_{18}O_4S_2$ [M + H]$^+$ 351.0725, found 351.0721.

*(Z)-3-Hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-3-m-tolylprop-2-ene-1-thione (**6h**):* obtained from 3-methylacetophenone (**4g**) and dithioester **5f** ((Het)Ar = N-methyl-2-pyrrolyl), red liquid (0.22 g, 84%); R_f = 0.7 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2949, 1731, 1562, 1387, 1232, 1058, 785; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.06 (s, 1H), 7.73−7.70 (m, 2H), 7.35−7.34 (m, 2H), 7.26 (s, 1H), 6.92 (d, J = 3.6 Hz, 2H), 6.19 (t, J = 3.6 Hz, 1H), 4.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 174.2, 140.7, 138.6, 135.8, 133.6, 132.7, 128.8, 127.3, 123.9, 115.0, 108.6, 107.8, 38.8, 21.6; HRMS (ESI) m/z calcd for $C_{15}H_{15}NOS$ [M + H]$^+$ 258.0953, found 258.0945.

*(Z)-3-Hydroxy-1-(1-methyl-1H-indol-3-yl)-3-(pyridin-3-yl)prop-2-ene-1-thione (**6i**):* obtained from 3-acetylpyridine (**4h**) and dithioester **5g** ((Het)Ar = N-methylindol-3-yl), brown solid (0.25 g, 86%); mp 105−106 °C; R_f = 0.4 (3/2 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1590, 1517, 1457, 1349, 822; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.2 (s, 1H), 9.16 (d, J = 1.6 Hz, 1H), 8.71 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.56−8.53 (m, 1H), 8.22 (dt, J = 8.4 Hz, 1.6 Hz, 1H), 7.96 (s, 1H), 7.42 (dd, J = 8.0 Hz, 3.2 Hz, 1H), 7.37−7.34 (m, 4H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 170.9, 151.9, 151.8, 147.8, 138.5, 134.3, 134.2, 134.0, 125.8, 125.6, 123.8, 123.7, 122.5, 122.4, 110.7, 33.8; HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2OS$ [M + H]$^+$ 295.0905, found 295.0897.

*(Z)-3-(Furan-2-yl)-3-hydroxy-1-(1-methyl-1H-indol-3-yl)prop-2-ene-1-thione (**6j**):* obtained from 2-acetylfuran (**4i**) and dithioester **5g**, red solid (0.17 g, 78%); mp 92−93 °C; R_f = 0.5 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3113, 2935, 1615, 1510, 1223, 743; ^1H NMR (400 MHz, $CDCl_3$) δ 15.81 (s, 1H), 8.55−8.53 (m, 1H), 7.96 (s, 1H), 7.62 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H), 7.42 (s, 1H), 7.36−7.34 (m, 3H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 164.6, 145.6, 138.4, 133.8, 125.7, 125.2, 123.5, 123.0, 122.5, 114.8, 112.9, 110.3, 105.5, 33.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_2S$ [M + H]$^+$ 284.0745, found 284.0739.

*(Z)-3-(Furan-2-yl)-3-hydroxy-1-(thiophen-2-yl)prop-2-ene-1-thione (**6k**):* obtained from 2-acetylfuran (**4i**) and dithioester **5e**, red solid (0.21 g, 90%); mp 94−95 °C; R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 3074, 1613, 1536, 1432, 1249, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 15.53 (s, 1H), 7.77 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.65 (dd, *J* = 1.6 Hz, 0.4 Hz, 1H), 7.62 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.39 (s, 1H), 7.25 (dd, *J* = 3.2 Hz, 0.4 Hz, 1H), 7.14 (dd, *J* = 4.8 Hz, 4.0 Hz, 1H), 6.61 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 166.2, 152.3, 149.8, 146.5, 134.2, 128.8, 127.7, 116.4, 113.3, 105.7; HRMS (ESI) *m/z* calcd for $C_{11}H_8O_2S_2$ [M + H]$^+$ 237.0044, found 237.0033.

*(Z)-3-Hydroxy-3-(pyridin-3-yl)-1-(thiophen-2-yl)prop-2-ene-1-thione (**6l**):* obtained from 3-acetylpyridine (**4h**) and dithioester **5e**, red solid (0.22 g, 92%); mp 115−116 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1589, 1260, 1018, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 15.91 (s, 1H), 9.17 (d, *J* = 2.0 Hz, 1H), 8.76 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 8.23 (dt, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.79 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.68 (dd, *J* = 5.0 Hz, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 7.39 (s, 1H), 7.16 (dd, *J* = 5.0 Hz, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 172.9, 153.1, 152.6, 148.1, 136.6, 135.2, 131.3, 129.6, 128.7, 124.4, 106.9; HRMS (ESI) *m/z* calcd for $C_{12}H_9NOS_2$ [M + H]$^+$ 248.0204, found 248.0211.

*(Z)-4-Hydroxy-4-(4-methoxyphenyl)but-3-ene-2-thione (**6m**):* obtained from 4-methoxyacetophenone (**4c**) and methyl dithioester **5h**, red liquid (0.13 g, 60%); R_f = 0.8 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2919, 1641, 1414, 1030, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 14.84 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.74 (s, 1H), 3.85 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 162.5, 136.9, 132.2, 128.8, 115.7, 113.9, 55.5, 28.0; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_2S$ [M + H]$^+$ 209.0636, found 209.0631.

*(2-Hydroxycyclopent-1-enyl)(phenyl)methanethione (**6n**):* obtained from cyclopentanone (**4j**) and dithioester **5a**, viscous liquid (0.15 g, 70%): R_f = 0.8 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2919, 1641, 1414, 1030, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.40−7.36 (m, 5H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.51 (t, *J* = 7.6 Hz, 2H), 1.80 (quin, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 151.9, 141.6, 129.2, 128.6, 127.4, 126.7, 40.3, 32.1, 19.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}OS$ [M + H]$^+$ 205.0687, found 205.0679.

*(1-Hydroxy-3,4-dihydronaphthalen-2-yl)(4-methoxyphenyl)-methanethione (**6o**).* obtained from 1-tetralone (**4k**) and dithioester **5b**, sticky solid (0.22 g, 72%): R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2934, 1602, 1503, 1248, 1176, 1039, 739; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.11 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.44 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.35 (td, *J* = 8.0 Hz, 1.2 Hz, 1H); 7.25 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.81−2.76 (m, 2H), 2.71−2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 172.1, 159.9, 142.5, 137.8, 133.3, 132.8, 128.5, 127.9, 127.8, 127.2, 124.5, 113.9, 55.5, 29.1, 29.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}O_2S$ [M + H]$^+$ 297.0949, found 297.0934.

General Procedure for the Preparation of 1-Aryl-3,5-bis(het)-arylpyrazoles 7 and 1,3-Bis(aryl)-4,5-annulated Pyrazoles 7n,o from Monothiodiketones 6. A solution of the respective 1,3-monothiodiketone **6** (5.0 mmol) and arylhydrazine (5.5 mmol) in 25 mL of EtOH was refluxed for 4 h with constant stirring (monitored by TLC). The reaction mixture was concentrated under reduced pressure, poured into water, extracted with DCM (3 × 50 mL), washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude pyrazoles **7**, which were purified by column chromatography over silica gel using EtOAc/hexane as eluent (Table 1).

*5-(4-Chlorophenyl)-1,3-diphenyl-1H-pyrazole (**7a**):* obtained from monothio-1,3-diketone **6a** and phenylhydrazine, white solid (1.52 g, 92%); mp 104−105 °C (lit.[16b] mp 104−105 °C); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1593, 1483, 1184, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.37−7.25 (m, 8H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 143.2, 139.7, 134.4, 132.6, 129.9, 129.0, 128.7, 128.2, 127.7, 125.8, 125.3, 105.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClN_2$ [M + H]$^+$ 331.1002, found 331.0997.

*5-(3-Bromophenyl)-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**7b**):* obtained from monothio-1,3-diketone **6b** and phenylhydrazine, yellow solid (1.74 g, 86%); mp 89−90 °C; R_f = 0.6 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 3066, 2833, 1690, 1252, 787; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.41−7.30 (m, 5H), 7.20−7.08 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 3.85(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.9, 142.6, 139.8, 132.7, 131.5, 131.2, 129.9, 129.0, 127.6, 127.3, 127.1, 125.5, 125.3, 122.5, 114.1, 105.1, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}BrN_2O$ [M + Na]$^+$ 427.0422, found 427.0424.

*1-(4-Chlorophenyl)-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (**7c**):* obtained from monothio-1,3-diketone **6c** and 4-chlorophenylhydrazine, white solid (1.55 g, 86%); mp 105−106 °C (lit.[32] mp 104−106 °C); R_f = 0.6 (1/9 EtOAc/hexane), IR (KBr, cm^{-1}) 3055, 2933, 1609, 1492, 1253, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.29−7.19 (m, 9H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.69 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 152.0, 144.4, 138.4, 133.0, 130.2, 129.0, 128.7, 128.6, 128.5, 127.1, 126.3, 125.2, 114.1, 105.1, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}ClN_2O$ [M + H]$^+$ 361.1108, found 361.1102.

*1,3-Diphenyl-5-(pyridin-4-yl)-1H-pyrazole (**7d**):* obtained from monothio-1,3-diketone **6d** and phenylhydrazine, pale yellow solid (1.28 g, 87%); mp 94−95 °C; R_f = 0.42 (3/7 EtOAc/hexane), IR (KBr, cm^{-1}) 3073, 1600, 1215, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.2 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.46−7.36 (m, 8H), 7.16 (d, *J* = 5.2 Hz, 2H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 150.1, 141.6, 139.7, 138.0, 132.5, 129.2, 128.7, 128.3, 128.2, 125.8, 125.5, 122.7, 106.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}N_3$ [M + Na]$^+$ 320.1164, found 320.1164.

*1-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)-5-(pyridine-4-yl)-1H-pyrazole (**7e**):* obtained from monothio-1,3-diketone **6e** and 4-bromophenylhydrazine, white solid (1.60 g, 73%); mp 74−76 °C; R_f = 0.4 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1595, 1201, 1046, 774; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.60 (br s, 2H), 7.46−7.35 (m, 7H), 6.87 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 152.3, 144.5, 141.9, 139.5, 132.8, 132.6, 132.0, 131.9, 131.7, 129.4, 129.2, 128.7, 125.8, 113.0, 105.8, 56.0, 55.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}BrN_3O_2$ [M + H]$^+$ 436.0661, found 436.0660

*5-(2,5-Dimethylphenyl)-1-(4-methoxyphenyl)-3-(thien-2-yl)-1H-pyrazole (**7f**):* obtained from monothio-1,3-diketone **6f** and 4-methoxyphenylhydrazine, pale yellow solid (1.42 g, 79%); mp 145−146 °C; R_f = 0.68 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2969, 1608, 1514, 1250, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.27 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.11−7.04 (m, 4H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.58 (s, 1H), 3.76 (s, 3H), 2.31 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 146.7, 143.8, 136.6, 135.3, 134.0, 133.5, 131.1, 130.4, 130.2, 129.8, 127.4, 125.0, 124.6, 123.9, 113.9, 105.6, 55.4, 20.8, 19.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_2OS$ [M + Na]$^+$ 383.1194, found 383.1187.

*5-(3-Methylthiophen-2-yl)-1-phenyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole (**7g**):* obtained from monothio-1,3-diketone **6g** and phenylhydrazine, yellow solid (1.54 g, 77%); mp 141−142 °C; R_f = 0.45 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2922, 1591, 1492, 1183, 768; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.87 (m, 5H), 7.32 (d, *J* = 4.8 Hz, 1H), 7.04 (s, 2H), 6.96 (d, *J* = 4.8 Hz, 1H), 6.63 (s, 1H), 3.91 (s, 6H), 3.89 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 147.3, 143.9, 140.0, 134.7, 131.2, 130.5, 129.8, 128.8, 128.8, 128.7, 128.5, 127.3, 123.4, 106.6, 61.6, 56.4, 15.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_2O_3S$ [M + H]$^+$ 407.1429, found 407.1434.

*1-(4-Methoxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)-5-m-tolyl-1H-pyrazole (**7h**):* obtained from monothio-1,3-diketone **6h** and 4-methoxyphenylhydrazine, red viscous liquid (1.63 g, 96%); R_f = 0.7

(1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1462, 1376, 723; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 5.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 3H), 7.30 (d, J = 7.2 Hz, 3H), 7.03 (s, 1H), 6.75 (d, J = 5.2 Hz, 2H), 6.55 (s, 1 H), 3.75 (s, 3H), 3.51 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 146.4, 144.3, 136.0, 135.2, 132.7, 129.5, 129.1, 128.8, 128.7, 128.4, 128.2, 127.8, 124.3, 123.9, 119.2, 107.1, 56.0, 33.2, 21.4; HRMS (ESI) m/z calcd for $C_{22}H_{21}N_3O$ [M + H] 344.1763, found 344.1771.

*1-Phenyl-3-(1-methyl-1H-indol-3-yl)-5-(pyridin-3-yl)-1H-pyrazole (**7i**):* obtained from monothio-1,3-diketone **6i** and phenylhydrazine, white solid (1.61 g, 92%); mp 151−152 °C; R_f = 0.5 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 3046, 2928, 1613, 1308, 1246, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.57 (br d, J = 3.8 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.57 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 7.54 (s, 1H), 7.39−7.21 (m, 9H), 6.87 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.4, 148.2, 139.8, 139.7, 137.3, 136.6, 129.2, 127.6, 127.5, 127.2, 126.0, 125.3, 123.5, 122.1, 121.2, 120.2, 109.4, 108.4, 106.1, 33.0; HRMS (ESI) m/z calcd for $C_{23}H_{18}N_4$ $[M + H]^+$ 351.1610, found 351.1603.

*5-(Furan-2-yl)-3-(1-methyl-1H-indol-3-yl)-1-(4-chlorophenyl)-1H-pyrazole (**7j**):* obtained from monothio-1,3-diketone **6j** and 4-chlorophenylhydrazine, viscous liquid (1.68 g, 90%); R_f = 0.5 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1614, 1495, 1224, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.8 Hz, 1H), 7.50 (s, 1H), 7.46−7.20 (m, 8H), 6.93 (s, 1H), 6.39 (dd, J = 3.4 Hz, 2.0 Hz, 1H), 6.16 (d, J = 3.4 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 144.4, 142.7, 139.1, 137.3, 134.7, 133.5, 129.1, 127.1, 126.7, 126.0, 122.1, 121.1, 120.1, 111.3, 109.2, 108.4, 104.5, 32.9; HRMS (ESI) m/z calcd for $C_{22}H_{16}ClN_3O$ 374.1060, found 374.1044.

*1-(4-Chlorophenyl)-5-(furan-2-yl)-3-(thiophen-2-yl)-1H-pyrazole (**7k**):* obtained from monothio-1,3-diketone **6k** and 4-chlorophenylhydrazine, colorless liquid (1.56 g, 96%); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 3114, 1494, 1088, 1038, 832, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.37 (m, 6H), 7.25−7.21 (m, 1H), 7.05−7.02 (m, 1H), 6.82 (s, 1H), 6.34−6.32 (m, 1H), 6.06 (br d, J = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 143.6, 142.8, 138.3, 135.6, 135.4, 134.2, 129.2, 127.5, 127.0, 125.1, 124.4, 111.3, 109.4, 103.7; HRMS (ESI) m/z calcd for $C_{17}H_{11}ClN_2OS$ $[M + H]^+$ 327.0359, found 327.0350.

*1-Phenyl-3-(thiophen-2-yl)-5-(pyridin-3-yl)-1H-pyrazole (**7l**):* obtained from monothio-1,3-diketone **6l** and phenylhydrazine, colorless viscous liquid (1.28 g, 84%); R_f = 0.5 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3067, 1595, 1498, 970, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59−8.55 (m, 2H), 7.49−7.44 (m, 2H), 7.39−7.21 (m, 7H), 7.10−7.07 (m, 1H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 149.2, 147.6, 140.9, 139.3, 135.7, 129.2, 128.0, 127.5, 126.4, 125.4, 125.1, 124.3, 123.1, 105.5; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3S$ $[M + H]^+$ 304.0908, found 304.0893.

*1-(4-Fluorophenyl)-5-(4-methoxyphenyl)-3-methyl-1H-pyrazole (**7m**):* obtained from monothio-1,3-diketone **6m** and 4-fluorophenylhydrazine, brown viscous liquid (1.13 g, 81%); R_f = 0.46 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2927, 2360, 1511, 1250, 837; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.19 (m, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.0 (t, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.24 (s, 1H), 3.85 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.1, 159.5, 149.4, 143.7, 136.4, 129.9, 129.4, 126.9, 126.8, 122.9, 115.8, 115.6, 113.9, 107.2, 55.2, 13.5; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN_2O$ $[M + H]^+$ 283.1247, found 283.1249.

*1,3-Diphenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole (**7n**):* obtained from monothio-1,3-diketone **6n** and phenylhydrazine, viscous liquid (0.88 g, 68%); R_f = 0.5 (1/19 EtOAc/hexane), IR (KBr, cm^{-1}) 3054, 2951, 1595, 1502, 1297, 1069, 752, 686; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 2H), 7.71 (d, J = 6.6 Hz, 2H), 7.41 (d, J = 6.1 Hz, 4H), 7.30 (s, 1H), 7.23 (d, J = 6.1 Hz, 1H), 3.02 (t, J = 6.6 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 145.6, 140.4, 133.7, 129.2, 128.5, 127.4, 127.0, 125.9, 125.4, 118.4, 30.9, 26.5, 24.2; HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2$ $[M + H]^+$ 261.1392, found 261.1394.

*3-(4-Methoxyphenyl)-1-phenyl-4,5-dihydro-1H-benzo[g]indazole (**7o**):* obtained from monothio-1,3-diketone **6o** and phenylhydrazine, semisolid (1.50 g, 85%); R_f = 0.6 (1/16 EtOAc/hexane), IR (KBr, cm^{-1}) 2929, 1599, 1466, 1248, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.2 Hz, 1H), 7.35−7.21 (m, 8H), 7.12 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.8, 140.4, 138.4, 136.9, 130.6, 129.6, 128.8, 128.3, 127.7, 126.8, 125.1, 122.6, 116.7, 113.9, 55.2, 29.7, 19.5; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2O$ $[M + H]^+$ 353.1654, found 353.1637.

*4-Ethyl-3-(4-methoxyphenyl)-1,5-diphenyl-1H-pyrazole (**7p**):* obtained from monothio-1,3-diketone **6p** and phenylhydrazine, colorless solid (1.32 g, 75%); mp 106−108 °C (lit.[15e] mp 104−106 °C); R_f = 0.6 (1/9 EtOAc/hexane), IR (KBr, cm^{-1}) 3050, 2931, 1600, 1501, 1249, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.8 Hz, 2H), 7.37−7.35 (m, 3H), 7.29−7.22 (m, 7H), 7.12 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.64 (q, J = 7.2 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 150.8, 141.3, 131.3, 130.3, 129.3, 128.7, 128.6, 128.4, 126.9, 126.7, 124.8, 120.8, 114.1, 55.4, 17.3, 15.7; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2O$ $[M + H]^+$ 355.1810, found 355.1805.

General Procedure for the Preparation of 1,3-Bis(het)aryl-3-(methylthio)-2-propenones 8. To a stirred suspension of NaH (1.1 mmol, 100%) in DMF (20 mL) under an N_2 atmosphere was added dropwise a solution of (het)aryl methyl ketone **4** (1 mmol) and (het)aryl dithioester **5** (1.2 mmol) in DMF (10 mL) at 0 °C, and the reaction mixture was further stirred at room temperature for 1 h. After complete formation of monothiodiketone **6** (monitored by TLC), the reaction mixture was cooled to 0 °C, followed by dropwise addition of methyl iodide (1.2 mmol) and further stirring at room temperature for 2 h (monitored by TLC). The mixture was then poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) followed by brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude products **8**, which were purified by column chromatography using hexane/EtOAc as eluent.

*(Z)-1-(4-Chlorophenyl)-3-(methylthio)-3-phenylprop-2-en-1-one (**8a**):* obtained from 4-chloroacetophenone (**4a**) and dithioester **5a**, yellow solid (0.28 g, 98%); mp 78−79 °C; R_f = (1/9 EtOAc/hexanes); IR (KBr, cm^{-1}) 2920, 1626, 1526, 1249, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.4 Hz, 2H), 7.36−7.30 (m, 5H), 7.23 (d, J = 7.4 Hz, 2H), 6.95 (s, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 165.9, 138.5, 138.4, 136.9, 129.4, 128.9, 128.8, 128.6, 127.9, 118.5, 16.6; HRMS (ESI) m/z calcd for $C_{16}H_{13}ClOS$ $[M + H]^+$ 289.0454, found 289.0439.

*(E/Z)-1-(3-Bromophenyl)-3-(4-methoxyphenyl)-3-(methylthio)-prop-2-en-1-one (**8b**):* obtained from 3-bromoacetophenone (**4b**) and dithioester **5b** (E/Z = 80/20), yellow semisolid (0.24 g, 67%); R_f = 0.4 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1604, 1503, 1247, 776; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, J = 1.6 Hz, 0.8H), 7.89 (m, 1H), 7.72 (m, 0.2H), 7.63−7.61 (m, 0.8H), 7.55−7.52 (m, 0.2H), 7.33−7.19 (m, 3H), 6.99 (s, 0.8H), 6.96 (d, J = 8.8 Hz, 1.6H), 6.80 (d, J = 8.8 Hz, 0.4H), 6.45 (s, 0.2H), 3.85 (s, 2.4H), 3.77 (s, 0.6H), 2.45 (s, 0.6H), 2.00 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 186.8, 166.3, 162.5, 160.7, 160.4, 141.1, 140.7, 135.0, 134.9, 131.7, 131.2, 131.1, 130.2, 130.1, 129.9, 129.7, 129.6, 127.0, 126.6, 122.9, 122.6, 118.5, 115.2, 114.2, 113.8, 55.5, 55.4, 17.0, 16.7; HRMS (ESI) m/z calcd for $C_{17}H_{15}BrO_2S$ $[M + H]^+$ 363.0054, found 363.0038.

*(Z)-1-(4-Methoxyphenyl)-3-(methylthio)-3-phenylprop-2-en-1-one (**8c**):* obtained from 4-methoxyacetophenone (**4c**) and dithioester **5a**, viscous semisolid (0.28 g, 95%); R_f = 0.5 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2925, 1602, 1533, 1241, 1170, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 7.46−7.39 (m, 3H), 7.34−7.32 (m, 2H), 7.06 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 163.5, 163.0, 139.0, 131.7, 130.4, 128.8, 128.7, 128.2, 119.4, 113.8, 55.5, 16.7; HRMS (ESI) m/z calcd for $C_{17}H_{16}O_2S$ $[M + H]^+$ 285.0949, found 285.0931.

*(Z)-3-(Methylthio)-3-phenyl-1-(pyridin-4-yl)prop-2-en-1-one (**8d**):* obtained from 4-acetylpyridine (**4d**) and dithioester **5a**, yellow solid (0.19 g, 72%); mp 101−102 °C; R_f = 0.5 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1731, 1524, 1247, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 6.0 Hz, 2H), 7.47−7.42 (m, 3H), 7.31−7.29 (m, 2H), 7.02 (s, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 168.5, 149.2, 145.0, 137.9, 128.1, 128.0, 127.5, 121.1, 117.5,

16.5; HRMS (ESI) m/z calcd for $C_{15}H_{13}NOS$ [M + H]$^+$ 256.0796, found 256.0780.

*(Z)-3-(3,4-Dimethoxyphenyl)-3-(methylthio)-1-(pyridin-4-yl)prop-2-en-1-one (**8e**):* obtained from 4-acetylpyridine (**4d**) and dithioester **5c**, yellow solid (0.23 g, 71%); mp 74−75 °C; R_f = 0.4 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 2835, 1602, 1503, 1248, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74−8.72 (m, 2H), 7.72−7.71 (dd, J = 4.4 Hz, 1.6 Hz, 2H), 7.01 (s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.88 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 6.81 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 168.1, 150.7, 149.9, 149.1, 144.8, 130.9, 121.1, 120.6, 117.8, 111.2, 111.1, 56.1, 56.0, 16.9; HRMS (ESI) m/z calcd for $C_{17}H_{17}NO_3S$ [M + H]$^+$ 316.1007, found 316.0993.

*(E/Z)-1-(2,5-Dimethylphenyl)-3-(methylthio)-3-(thiophen-2-yl)-prop-2-en-1-one (**8f**):* obtained from 2,5-dimethylacetophenone (**4e**) and dithioester **5e** (E/Z = 70/30), yellow semisolid (0.21 g, 75%); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2920, 1633, 1543, 1247, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 6.4 Hz, 0.7H), 7.37 (s, 0.7H), 7.21 (d, J = 4.0 Hz, 1.4H), 7.16−7.07 (m, 2.5H), 7.00 (d, J = 5.2 Hz, 0.7H), 6.97 (s, 0.7H), 6.83 (t, J = 4.0 Hz, 0.3H), 2.42 (s, 2.1H), 2.40 (s, 0.9H), 2.33 (s, 0.9H), 2.32 (s, 2.1H), 2.26 (s, 0.9H), 2.22 (s, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 192.5, 153.4, 150.8, 140.4, 139.6, 139.2, 138.2, 135.2, 134.7, 134.6, 134.4, 131.6, 131.5, 131.3, 131.2, 129.5, 129.3, 129.1, 128.5, 128.3, 127.6, 127.5, 127.1, 124.0, 120.9, 21.0, 20.8, 20.4, 20.2, 17.5, 17.0; HRMS (ESI) m/z calcd for $C_{16}H_{16}OS_2$ [M + H]$^+$ 289.0721, found 289.0716.

*(Z)-3-(Methylthio)-1-(3-methylthiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**8g**):* obtained from 2-acetyl-3-methylthiophene (**4f**) and dithioester **5d**, yellow solid (0.29 g, 78%); mp 109−110 °C; R_f = 0.6 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2935, 1612, 1498, 1241, 1126, 811; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 4.8 Hz, 1H), 6.88 (s, 1H), 6.76 (d, J = 4.8 Hz, 1H), 6.51 (s, 2H), 3.89 (s, 6H), 3.88 (s, 3H), 2.52 (s, 3H), 2.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 163.2, 153.5, 149.1, 144.1, 138.5, 134.2, 131.1, 126.8, 118.9, 105.4, 61.1, 56.5, 16.7, 16.2; HRMS (ESI) m/z calcd for $C_{18}H_{20}O_4S_2$ [M + H]$^+$ 365.0881, found 365.0873.

*(E/Z)-3-(1-Methyl-1H-pyrrol-2-yl)-3-(methylthio)-1-m-tolylprop-2-en-1-one (**8h**):* obtained from 3-methylacetophenone (**4g**) and dithioester **5f** (E/Z = 66/34). yellow viscous liquid (0.57 g, 60%); R_f = 0.5 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}): 2920, 1632, 1513, 1254, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.75 (m, 1.32H), 7.68 (t, J = 3.6 Hz, 0.68H), 7.33 (dd, J = 4.8 Hz, 0.8 Hz, 1.32H), 7.29 (dd, J = 3.2 Hz, 2.0 Hz, 0.68H), 7.18 (s, 0.66H), 6.73 (dd, J = 2.4 Hz, 2.0 Hz, 0.66H), 6.70−6.68 (m, 0.68H), 6.35 (dd, J = 3.6 Hz, 1.6 Hz, 0.34H), 6.21 (dd, J = 3.6 Hz, 2.0 Hz, 0.66H), 6.17 (dd, 3.6 Hz, 2.8 Hz, 0.66H), 6.12 (dd, J = 3.6 Hz, 2.4 Hz, 0.34H), 3.62 (s, 1.98H), 3.44 (s, 1.02H), 2.44 (s, 1.02H), 2.40 (s, 1.98H), 2.38 (s, 1.02H), 1.91 (s, 1.98H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 187.8, 155.4, 152.2, 139.3, 138.7, 138.4, 138.2, 133.2, 133.0, 130.4, 129.0, 128.9, 128.7, 128.5, 128.3, 125.9, 125.4, 125.3, 124.2, 120.7, 116.0, 112.5, 110.5, 108.3, 108.0, 34.3, 34.1, 21.5, 21.4, 16.8, 15.7; HRMS (ESI) m/z calcd for $C_{16}H_{17}NOS$ [M + H]$^+$ 272.1109, found 272.1103.

*(E/Z)-3-(1-Methyl-1H-indol-3-yl)-3-(methylthio)-1-(pyridin-3-yl)-prop-2-en-1-one (**8i**):* obtained from 3-acetylpyridine (**4h**) and dithioester **5g** (E/Z = 70/30), yellow viscous liquid (0.30 g, 96%); R_f = 0.4 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}): 2922, 1514, 1237, 1018, 743; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 0.7H), 8.85 (s, 0.3H), 8.63 (d, J = 3.4 Hz, 0.7H), 8.39 (s, 0.3H), 8.22 (d, J = 8.0 Hz, 0.7H), 7.91 (d, J = 8.0 Hz, 0.3H), 7.21 (d, J = 8.0 Hz, 0.7H), 7.35−6.99 (m, 6.0H), 6.42 (s, 0.3H), 3.78 (s, 2.1H), 3.64 (s, 0.3H), 2.44 (s, 0.3H), 2.11 (s, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 186.1, 160.5, 156.7, 151.7, 150.1, 148.8, 147.9, 137.1, 137.0, 136.3, 135.7, 135.2, 134.5, 131.5, 129.0, 126.1, 125.7, 123.7, 123.0, 122.8, 122.6, 121.1, 120.8, 120.6, 120.1, 117.1, 114.1, 113.7, 112.9, 109.9, 109.6, 33.1, 29.6, 17.3, 16.8; HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2OS$ [M + H]$^+$ 309.1062, found 309.1048.

*(E/Z)-1-(Furan-2-yl)-3-(1-methyl-1H-indol-3-yl)-3-(methylthio)-prop-2-en-1-one (**8j**):* obtained from 2-acetylfuran (**4i**) and dithioester **5g** (E/Z = 75/25), yellow viscous liquid (0.28 g, 92%); R_f = 0.4 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1622, 1517, 1253, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 0.75H), 7.53 (s, 0.75H), 7.51 (d, J = 7.8 Hz, 0.25H), 7.37−7.10 (m, 6H), 6.74 (s, 0.25H), 6.51 (dd, J = 3.2 Hz, 1.6 Hz, 0.75H), 6.49 (dd, J = 3.2 Hz, 1.6 Hz, 0.25H), 3.85 (s, 2.25H), 3.80 (s, 0.75H), 2.52 (s, 0.75H), 2.17 (s, 2.25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.0, 154.7, 145.2, 137.3, 132.0, 129.2, 122.9, 121.1, 120.5, 117.7, 115.5, 114.5, 112.3, 111.8, 109.9, 33.3, 17.5; HRMS (ESI) m/z calcd for $C_{17}H_{15}NO_2S$ [M + H]$^+$ 298.0902, found 298.0887.

*(Z)-1-(Furan-2-yl)-3-(methylthio)-3-(thiophen-2-yl)prop-2-en-1-one (**8k**):* obtained from 2-acetylfuran (**4i**) and dithioester **5e**, yellow viscous liquid (0.23 g, 96%); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2992, 1627, 1569, 1256, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.40 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.20 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.18 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.15 (s, 1H), 7.08 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 6.51 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 155.0, 154.2, 145.7, 140.2, 128.4, 127.63, 127.59, 119.6, 116.1, 112.4, 17.6; HRMS (ESI) m/z calcd for $C_{12}H_{10}O_2S_2$ [M + H]$^+$ 251.0200, found 251.0193.

*(Z)-3-(Methylthio)-1-(pyridin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one (**8l**):* obtained from 3-acetylpyridine (**4h**) and dithioester **5e**, yellow viscous liquid (0.234 g, 90%), R_f = 0.4 (1/3 EtOAc/hexane); IR (KBr, cm^{-1}) 2922, 1632, 1506, 1250, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 8.73 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.25 (dt, J = 8.0 Hz, 2.0 Hz, 1H), 7.42 (dd, J = 4.2 Hz, 1.2 Hz, 1H), 7.40 (ddd, J = 8.0 Hz, 4.8 Hz, 0.8 Hz, 1H), 7.22 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.21 (s, 1H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 157.3, 152.8, 149.5, 139.8, 135.6, 134.0, 128.7, 127.9, 127.8, 123.7, 119.6, 17.6; HRMS (ESI) m/z calcd for $C_{13}H_{11}NOS_2$ [M + H]$^+$ 262.0360, found 262.0357.

*(Z)-1-(4-Methoxyphenyl)-3-(methylthio)but-2-en-1-one (**8m**):* obtained from 4-methoxyacetophenone (**4c**) and dithioester **5h**, yellow viscous liquid (0.20 g, 86%); R_f = 0.7 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2954, 1652, 1245, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2H), 7.04 (s, 1H), 6.97 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 2.07 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.8, 163.6, 138.1, 128.9, 126.0, 113.5, 107.9, 55.5, 24.4, 20.3; HRMS (ESI) m/z calcd for $C_{12}H_{14}O_2S$ [M + H]$^+$ 223.0793, found 223.0785.

*2-[(Methylthio)phenyl(methylene)]cyclopentanone (**8n**):* obtained from cyclopentanone (**4j**) and dithioester **5a**, viscous semisolid (0.16g, 74%); R_f = 0.4 (1/19 EtOAc/hexane); IR (KBr, cm^{-1}) 2925, 1699, 1571, 1243, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.2 Hz, 2H), 2.43 (t, J = 7.6 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.87 (t, J = 7.6 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 151.2, 137.2, 130.0, 128.8, 128.0, 127.5, 40.0, 31.5, 20.5, 15.4; HRMS (ESI) m/z calcd for $C_{13}H_{14}OS$ [M + H]$^+$ 219.0844, found 219.0844.

*(Z)-2-[(4-Methoxyphenyl)(methylthio)methylene]-3,4-dihydro-naphthalen-1(2H)-one (**8o**):* obtained from 1-tetralone (**4k**) and dithioester **5b**, yellow solid (0.3 g, 96%); mp 72−73 °C; R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2922, 1607, 1503, 1236, 1029, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.08−7.06 (m, 2H), 7.00−6.97 (m, 2H), 3.86 (s, 3H), 2.82 (t, J = 6.8 Hz, 2H), 2.54 (t, J = 6.8 Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 159.1, 156.3, 142.6, 134.5, 132.5, 129.7, 129.1, 127.9, 127.8, 126.9, 114.2, 55.3, 30.0, 29.4, 16.8; HRMS (ESI) m/z calcd for $C_{19}H_{18}O_2S$ [M + H]$^+$ 311.1106, found 311.1090.

General Procedure for the Preparation of Regioisomeric 1-Aryl-3,5-bis(het)arylpyrazoles 9 and 1,5-Bis(aryl)-3,4-annulated pyrazoles 9n,o from β-(Methylthio)-1,3-substituted/annulated Enones 8. *Method A.* A solution of respective β-(methylthio)enone **8** (5 mmol) in *tert*-butyl alcohol (10 mL) was added to a stirred suspension of the respective arylhydrazine (5.5 mmol) and *t*-BuOK (5.5 mmol) in *t*-BuOH (25 mL) at room temperature followed by further refluxing for 6−12 h (monitored by TLC). The solvent was evaporated under reduced pressure, and the residue was diluted with saturated NH_4Cl solution (1 × 50 mL) and extracted with DCM (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (1 × 50 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give crude pyrazoles **9**, which were purified by column chromatography over silica gel using EtOAc/hexane as eluent (Table 2).

Method B. To a stirred suspension of NaH (2 mmol, 100%) in DMF (20 mL) under an N_2 atmosphere was added a solution of the appropriate (hetero)aryl methyl ketone **4** (1 mmol) in DMF, followed by dropwise addition of the corresponding (het)aryl dithioester **5** (1.2 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 1 h (monitored by TLC), followed by addition of methyl iodide (1.2 mmol) at 0 °C, and stirring was further continued for 1 h at room temperature (monitored by TLC). The appropriate arylhydrazine (1.1 mmol) was then added to the reaction mixture followed by heating at 90 °C for 4−6 h along with stirring (monitored by TLC). The mixture was then poured into ice-cold water (1 × 50 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with H_2O (2 × 50 mL) and brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude adduct, which was purified by column chromatography using hexane/EtOAc as eluent (Table 2).

*3-(4-Chlorophenyl)-1,5-diphenyl-1H-pyrazole (**9a**):* obtained from β-(methylthio)enone **8a** and phenylhydrazine, brown solid (1.44 g, 87%); R_f = 0.5 (1/12 EtOAc/hexane); mp 145−146 °C (lit.[16b] mp 146−147 °C); IR (KBr, cm^{-1}) 2924, 1593, 1493, 1087, 765; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.35−7.25 (m, 10H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.8, 140.2, 133.9, 131.8, 130.6, 129.1, 129.0, 128.9, 128.7, 128.6, 127.7, 127.2, 125.4, 105.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClN_2$ $[M + H]^+$ 331.1002, found 331.0986.

*3-(3-Bromophenyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**9b**):* obtained from β-(methylthio)enone **8b** and phenylhydrazine, dark yellow solid (1.44 g, 72%): R_f = 0.62 (1/4 EtOAc/hexane); mp 75−76 °C; IR (KBr, cm^{-1}) 2923, 1458, 1375, 673; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.46−7.44 (m, 1H), 7.37−7.28 (m, 6H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 150.4, 144.5, 140.1, 135.3, 134.9, 130.8, 130.3, 130.1, 130.0, 129.4, 128.9, 127.5, 125.3, 124.3, 114.0, 104.7, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}BrN_2O$ $[M + Na]^+$ 427.0422, found 427.0424 .

*1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (**9c**):* obtained from β-(methylthio)enone **8c** and 4-chlorophenylhydrazine, white solid (1.48 g, 82%); mp 124−125 °C, R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1612, 1495, 1251, 1031, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.36−7.33 (m, 3H), 7.30−7.26 (m, 6H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 152.1, 144.3, 138.6, 132.9, 132.7, 130.0, 129.0, 128.6, 128.1, 126.3, 125.8, 122.5, 114.0, 105.0, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}ClN_2O$ $[M + H]^+$ 361.1108, found 361.1103.

*1,5-Diphenyl-3-(pyridin-4-yl)-1H-pyrazole (**9d**):* obtained from β-(methylthio)enone **8d** and phenylhydrazine, yellow solid (1.23 g, 82%); mp 106−107 °C; R_f = 0.35 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}) 3028, 1603, 1494, 1211, 799; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4 Hz, 2H), 7.79 (d, *J* = 4 Hz, 2H), 7.36−7.33 (m, 8H), 7.28−7.27 (m, 2H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.4, 145.0, 140.4, 139.9, 130.1, 129.0, 128.7, 128.6, 127.9, 125.3, 122.9, 120.1, 105.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}N_3$ $[M + H]^+$ 298.1344, found 298.1350.

*1-(4-Bromophenyl)-5-(3,4-dimethoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazole (**9e**):* obtained from β-(methylthio)enone **8e** and 4-bromophenylhydrazine, yellow solid (1.74 g, 83%); mp 94−95 °C; R_f = 0.37 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3063, 2923, 1594, 1181, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 6.0 Hz, 2H), 7.77 (d, *J* = 6.0 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.85−6.84 (m, 3H), 6.72 (s, 1 H), 3.90 (s, 3 H), 3.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 149.7, 149.1, 145.1, 140.4, 139.1, 132.2, 126.9, 122.4, 121.8, 121.6, 120.2, 112.0, 111.4, 105.6, 56.1, 55.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}BrN_3O_2$ $[M + H]^+$ 436.0661, found 436.0661.

*3-(2,5-Dimethylphenyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1H-pyrazole (**9f**):* obtained from β-(methylthio)enone **8f** and 4-methoxyphenylhydrazine, pale yellow solid (1.60 g, 94%); mp 152−153 °C; R_f = 0.68 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2959, 1609, 1518, 1247, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.94−6.87 (m, 4H), 6.87 (s, 1H), 6.70 (s, 1H), 3.85 (s, 3H), 2.52 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 152.1, 137.3, 135.2, 133.0, 132.9, 132.4, 131.7, 130.7, 129.9, 128.6, 127.7, 127.3, 127.0, 126.2, 114.1, 107.3, 55.5, 20.9, 20.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_2OS$ $[M + Na]^+$ 383.1194, found 383.1195.

*3-(3-Methylthiophen-2-yl)-1-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (**9g**):* obtained from β-(methylthio)enone **8g** and phenylhydrazine, white solid (1.66 g, 83%); mp 124−126 °C; R_f = 0.45 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 3051, 2946, 1571, 1449, 765; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 7.18 (d, *J* = 5.2 Hz, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 6.67 (s, 1H), 6.45 (s, 2H), 3.86 (s, 3H), 3.67 (s, 6H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.3, 143.9, 140.1, 138.3, 134.9, 131.3, 129.9, 128.9, 127.6, 125.7, 125.6, 123.6, 106.3, 106.2, 61.1, 56.1, 15.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_2O_3S$ $[M + H]^+$ 407.1429, found 407.1431.

*1-(4-Methoxyphenyl)-5-(1-methyl-1H-pyrrol-2-yl)-3-m-tolyl-1H-pyrazole (**9h**):* obtained from β-(methylthio)enone **8h** and 4-methoxyphenylhydrazine, viscous liquid (1.54 g, 93%): R_f = 0.71 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1462, 1376, 723; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 6.8 Hz, 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.80−7.95 (m, 3 H), 7.48−7.56 (m, 2 H), 7.41−7.34 (m, 2 H), 7.30−7.27 (m, 2 H), 6.95 (t, *J* = 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.53 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 145.8, 141.5, 139.6, 138.0, 132.5, 129.3, 129.1, 129.0, 128.8, 128.2, 125.8, 125.3, 122.7, 120.7, 115.6, 106.0, 58.1, 33.3, 20.0; HRMS (ESI) *m/z* calcd for $C_{22}H_{21}N_3O$ $[M + H]^+$ 344.1763, found 344.1765.

*1-Phenyl-3-(pyridin-3-yl)-5-(1-methyl-1H-indol-3-yl)-1H-pyrazole (**9i**):* obtained from β-(methylthio)enone **8i** and phenylhydrazine, off-white solid (1.58 g, 90%); mp 145−146 °C; R_f = 0.6 (1/1 EtOAc/hexane); IR (KBr, cm^{-1}) 2924, 1644, 1238, 1499, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (dd, *J* = 2.0 Hz, 0.8 Hz, 1H), 8.58 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.27 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50−7.47 (m, 2H), 7.38−7.28 (m, 6H), 7.16−7.17 (m, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 149.0, 147.5, 140.6, 139.1, 136.8, 133.1, 129.4, 129.1, 128.5, 127.8, 126.6, 125.4, 123.7, 122.5, 120.5, 120.1, 109.7, 104.9, 104.6, 33.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_4$ $[M + H]^+$ 351.1610, found 351.1595.

*5-(1-Methyl-1H-indol-3-yl)-3-(furan-2-yl)-1-(4-chlorophenyl)-1H-pyrazole (**9j**):* obtained from β-(methylthio)enone **8j** and 4-chlorophenylhydrazine, viscous liquid (1.61 g, 86%); R_f = 0.5 (1/4 EtOAc/hexane); IR (KBr, cm^{-1}) 2923, 1594, 1494, 1329, 890, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.30−7.26 (m, 3H), 7.16−7.12 (m, 1H), 6.82 (s, 1H), 6.80−6.79 (m, 2H), 6.49 (dd, *J* = 3.2 Hz, 2.0 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 145.1, 142.2, 139.1, 138.5, 136.9, 133.2, 129.1, 128.5, 126.5, 122.7, 120.6, 120.0, 111.5, 109.7, 106.5, 104.9, 104.6, 33.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}ClN_3O$ 374.1060, found 374.1054.

*1-(4-Chlorophenyl)-3-(furan-2-yl)-5-(thiophen-2-yl)-1H-pyrazole (**9k**):* obtained from β-(methylthio)enone **8k** and 4-chlorophenylhydrazine, viscous liquid (1.53 g, 94%); R_f = 0.6 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 2925, 1495, 1152, 1089, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 0.8 Hz, 1H), 7.38 (br s, 4H), 7.32 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 6.87 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 6.79 (s, 1H), 6.76 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 6.49 (dd, *J* = 3.6 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.9, 142.4, 138.3, 138.1, 134.3, 130.7, 129.3, 127.8, 127.6, 127.5, 127.1, 111.5, 106.8, 105.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{11}ClN_2OS$ $[M + H]^+$ 327.0359, found 327.0357.

*1-Phenyl-3-(pyridin-3-yl)-5-(thiophen-2-yl)-1H-pyrazole (**9l**):* obtained from β-(methylthio)enone **8l** and phenylhydrazine, white solid (1.19 g, 78%); mp 107−108 °C; R_f = 0.5 (1/3 EtOAc/hexane); IR (KBr, cm^{-1}) 3057, 1594, 1498, 957, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.58 (dd, *J* = 4.8 Hz, 1.4 Hz, 1H), 8.20 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 7.45−7.26 (m, 7H), 6.98−6.86 (m, 2H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 149.0, 147.3, 139.6, 138.6, 133.0, 130.8, 129.1, 128.8, 128.6, 127.5, 127.4, 126.8, 126.2, 123.6, 104.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{13}N_3S$ $[M + H]^+$ 304.0908, found 304.0899.

*1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-5-methyl-1H-pyrazole (**9m**):* obtained from β-(methylthio)enone **8m** and 4-fluorophenylhydrazine, white solid (1.18 g, 84%); mp 88−90 °C; IR (KBr, cm^{-1}) 2922,

1580, 1403, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.48 (dd, J = 8.4 Hz, 4.8 Hz, 2H), 7.16 (t, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.44 (s, 1H), 3.84 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.5, 159.5, 151.4, 140.1, 136.2, 136.1, 127.0, 126.9, 126.8, 126.0, 116.0, 115.8, 114.0, 103.9, 55.3, 12.4; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN_2O$ [M + H]$^+$ 283.1247, found 283.1243.

*2,3-Diphenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazole (**9n**):* obtained from β-(methylthio)enone **8n** and phenylhydrazine, viscous liquid (0.86 g, 66%); R_f = 0.7 (1/16 EtOAc/hexane); IR (KBr, cm^{-1}) 3059, 2952, 1596, 1506, 1362, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 10H), 2.85 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.50 (quin, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.0, 140.8, 136.2, 130.9, 128.8, 128.5, 128.4, 127.6, 126.7, 125.0, 29.9, 24.8, 23.7; HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2$ [M + H]$^+$ 261.1392, found 261.1390.

*3-(4-Methoxyphenyl)-2-phenyl-4,5-dihydro-2H-benzo[g]indazole (**9o**):* obtained from β-(methylthio)enone **8o** and phenylhydrazine, white solid (1.44 g, 82%); mp 118−119 °C; R_f = 0.5 (1/16 EtOAc/hexane); IR (KBr, cm^{-1}) 2929, 1599, 1465, 1248, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2 Hz, 1H), 7.35−7.21 (m, 8H), 7.12 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.98 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.0, 140.6, 138.6, 137.1, 130.8, 129.8, 128.9, 128.5, 127.9, 127.0, 125.2, 122.9, 122.8, 116.9, 114.1, 55.4, 29.9, 19.7; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2O$ [M + H]$^+$ 353.1654, found 353.1640.

*4-Ethyl-5-(4-methoxyphenyl)-1,3-diphenyl-1H-pyrazole (**9p**):* obtained from monothio-1,3-diketone **6q** and phenylhydrazine, colorless solid (1.23 g, 70%); mp 110−111 °C (lit.[19a] mp 110−111 °C); R_f = 0.5 (1/9 EtOAc/hexane); IR (KBr, cm^{-1}) 3056, 2960, 1610, 1554, 1453, 1280, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H), 7.37 (t, J = 7.0 Hz, 1H), 7.24−7.24 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 3.81(s, 3H), 2.64 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 150.7, 141.0, 140.1, 134.1, 131.3, 128.6, 128.4, 127.9, 127.6, 126.5, 124.6, 123.1, 120.7, 114.0, 55.2, 17.1, 15.6; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2O$ [M + H]$^+$ 355.1810, found 355.1805.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR and ^{13}C NMR spectra and ORTEP X-ray crystal structure displays and CIF files giving crystallographic data for **7a,d,i** and **9a,d,i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Alan R. Katritzky on his 85th birthday.

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