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Oxone-DMSO Triggered Methylene Insertion and C(sp²)—C(sp³)-H—C(sp²) Bond Formation to Access Functional Bis-Heterocycles

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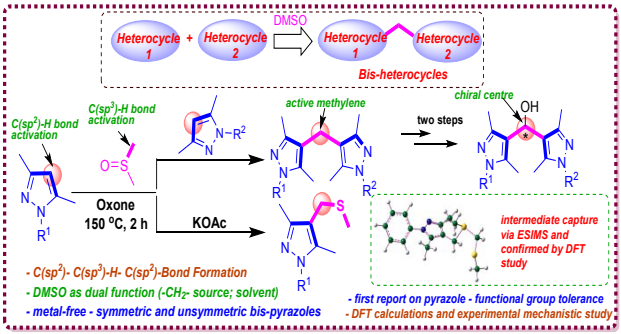
Supporting Information Placeholder



ABSTRACT: Metal-free insertion of methylene group was achieved for construction of new C(sp²)—C(sp³)-H—C(sp²) bond to get the novel bis-heterocyclic scaffolds. The complete mechanistic investigations included experimental study and DFT calculations and various symmetric as well as unsymmetric bis-pyrazoles and other pyrazole based bis-heterocyclic molecules were prepared in moderate to high yields. Further modification of bridged methylene group in unsymmetric pyrazoles generated a chiral centre to extend the scope of this method.

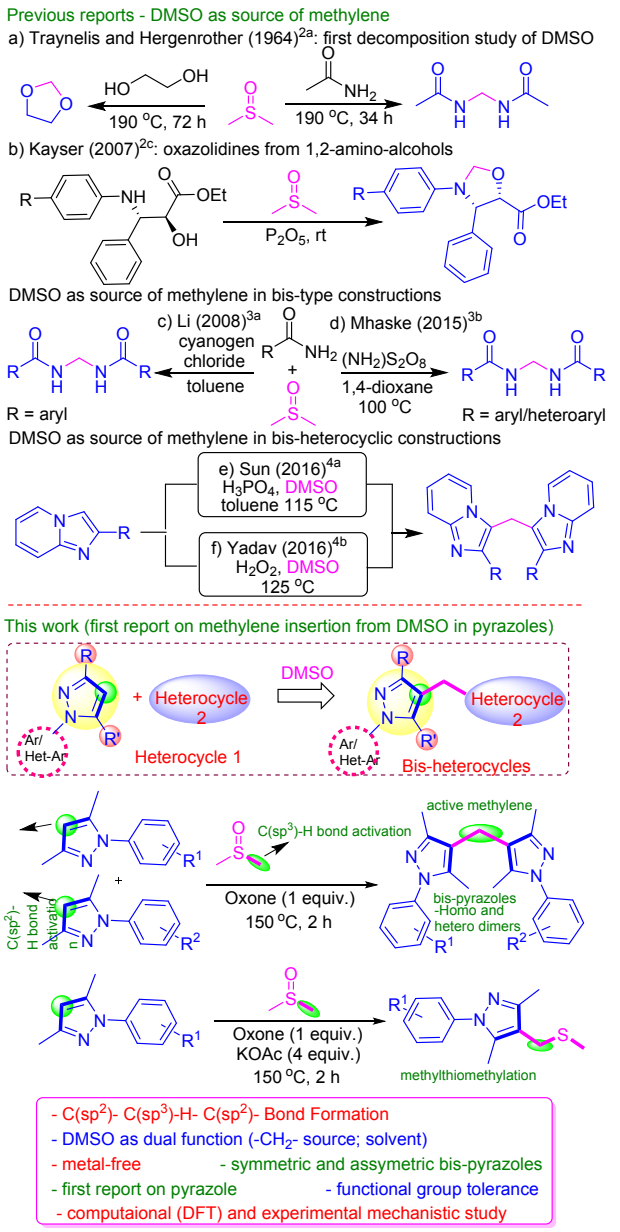
INTRODUCTION

Dimethyl sulfoxide (DMSO) has been recognized for its function as a high boiling reaction medium in organic synthesis due to easy accessibility, low reactivity, high polarity and high stability.[1] Being one of the least reactive solvent, its activation as a reagent attracts many synthetic chemists. Since from its decomposition studies observed by Traynelis and Hergenrother[2a] numerous methods have developed for its usage as synthone[2-4] for the installation of key functionalities in organic synthesis such as -CH_2SMe, –Me, -CH_2, =CH, –CHO, –CN, –SMe, -SO_2Me, etc. Li and Mhaske have synthesized bis-type of molecules from various amides using DMSO as a source of methylene promoted by cyanogen chloride[3a] and ammonium persulfate,[3b] respectively (Scheme 1c and 1d). Recently, DMSO has also been explored as a source of methylene for the construction of bis-heterocyclic scaffolds (Scheme 1e and 1f) using H_3PO_4[4a] and H_2O_2.[4b] The insertion of methylene is highly attractive synthetic strategy for assembling the functional molecules. Herein, we have disclosed a new method for insertion of methylene in C—C bond formation to access divergent bis-heterocyclic molecules.

The methyl group of DMSO was activated by oxone and inserted in between the two C(sp²)-H bonds of two same or different pyrazole moieties or pyrazole and other heterocyclic moiety. DMSO acts as a solvent as well as the source of methylene in the present oxone mediated transformation to supply various symmetric and unsymmetric bis-pyrazoles. Apart from bis-pyrazoles, further thriving extension to other heterocyclic scaffolds, presented the generality of this method. The use of DMSO is advantageous as compared to other carbon donor solvents because it is produced from the renewable process in the paper production industry. It is synthesized from dimethylsulfide which is the byproduct of

the kraft process. DMSO is very low toxic to human and environment.

Scheme 1. DMSO in methylene insertion for construction of various scaffolds

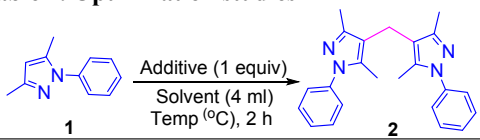


Pyrazoles[5] are privileged scaffold in various drugs and pharmacologically active molecules and introduction of bis-type of heterocyclic scaffolds particularly pyrazoles6 in a molecules has been recognized advantageous for potential relevance against Alzhimer's disease,[6a] for neuroprotective properties,[6d] and employed as the ligands[7] for the synthesis of molecular organic frameworks (MOFs).

RESULTS AND DISCUSSION

Our continued interest in development of metal-free methods[8] and further to extend our recent work on synthesis of 1,3,5-trisubstituted pyrazoles and dihydropyrazoles,[9] we start our studies on optimization towards activation of DMSO for the construction of bis-pyrazole scaffold. We commenced our studies with 3,5-dimethyl-1-phenyl-1*H*-pyrazole as a model substrate and DMSO as a source of methylene and systematically tested the reaction temperature, additive x, and solvents (Table 1). The optimization experiments revealed that the model reaction did not start at room temperature and even upto 100 °C (entries 1 and 2). Increasing the temperature upto 120 °C initiated the reaction and conferred the desired bis-pyrazole product to moderate yield (entry 3). Further increasing the temperature to 150 °C, afforded the desired product in good yield, however, refluxing conditions slightly improve the yield of product (entries 4 and 5). Apart from oxone, other additives which are known for their oxidizing properties such as TBHP, HTIB, H_2O_2, *m*-CPBA, and DDQ were also tested on the model substrate with DMSO, however, none of these was found to be more efficient in terms of the yield of the desired product (entries 6-10). I_2 completely suppress the reaction product (entry 11). Hence, oxone was found to be most suitable additive (oxidant) for the activation of DMSO at 150 °C, however, other solvents bearing methyl or methylene moiety such as DMF, PEG-200, ethylene glycol, MeOH, MeCN,

Table 1. Optimization studies[a]



entry	additive x	solvent	temp. (°C)	yield[b] (%)
1	Oxone	DMSO	rt	0
2	Oxone	DMSO	100	0
3	Oxone	DMSO	120	40
4	Oxone	DMSO	150	71
5	Oxone	DMSO	reflux	72 (73)[c]
6	TBHP	DMSO	150	31
7	HTIB	DMSO	150	62
8	H_2O_2	DMSO	150	26
9	*m*CPBA	DMSO	150	20
10	DDQ	DMSO	150	40
11	I_2	DMSO	150	0
12	Oxone	DMF	reflux	traces
13	Oxone	PEG-200	reflux	0
14	Oxone	Ethylene glycol	reflux	0
15	Oxone	MeOH	reflux	0
16	Oxone	MeCN	reflux	0
17	Oxone	DCM	reflux	0
18	Oxone	Xylene	reflux	0
19	Oxone	H_2O	reflux	0
20	Oxone	PMSO	reflux	45
21[d]	Oxone	DESO	reflux	35 (9)[e]

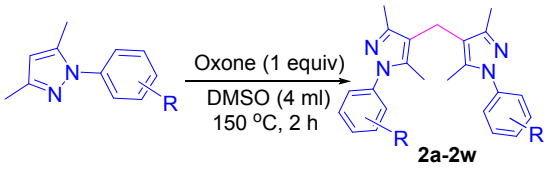
[a]Reaction conditions: 1 (1 mmol), additive (1 equiv) in solvent (4 ml) were stirred at 150 °C for 2 h. [b]Isolated yields. [c]Reaction time 12 h. [d]LCMS based concentration. [e]ethylene insertion product. PMSO = phenylmethylsulfoxide; DESO = diethylsulfoxide

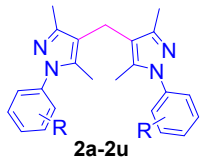
DCM and xylene were not activated under these conditions to offer methylene source for the construction of bis-pyrazole (entries 12-18). Only traces of desired product was observed, when DMF was used as solvent (entry 12), and obviously, reaction did not proceed in absence of non methylated solvents such as H_2O without DMSO (entry 19). Increasing the reaction time did not improve the yield of the desired product (entry 5). Reaction was also applicable to other sulfoxides such as phenylmethyl sulfoxide (entry 20) and diethylsulfoxide (entry 21). However, in case of diethylsulfoxide, in addition to methyl insertion, ethylene insertion was also observed (entry 21).

Having established the optimization of reaction conditions, we examined the scope of developed method to explore the generality of the reaction. In order to synthesize symmetric

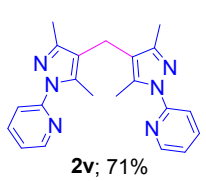
bis-pyrazoles, various pyrazole derivatives bearing diverse substitutions on phenyl ring were reacted with DMSO under optimal reaction conditions (Table 2). Mono- and di-halogen atoms, irrespective to their positions (*o*-, *m*-, *p*-), were well tolerated on the phenyl ring and afforded corresponding symmetric bis-pyrazoles in reasonable yields along with the simple phenyl ring derivative (**2a-2l**).

Table 2. Substrate scope for synthesis of symmetric bis-pyrazoles[a,b]



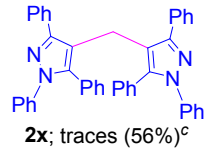


2a, R = H; 71% (54%)[e]
2b, R = *o*-F; 64%
2c, R = *m*-F; 66%
2d, R = *p*-F; 69%
2e, R = *o*-Cl; 65%
2f, R = *m*-Cl; 65%
2g, R = *p*-Cl; 78%
2h, R = *o*-Br; 63%
2i, R = *m*-Br; 68%
2j, R = *p*-Br; 80%
2k, R = *o*-F, *p*-F; 61%
2l, R = *o*-Cl, *p*-Cl; 63%
2m, R = *o*-CH_3; 72%
2n, R = *m*-CH_3; 73%
2o, R = *p*-CH_3; 74%
2p, R = *m*-CH_3, *p*-CH_3; 76%
2q, R = *m*-CF_3; 71%
2r, R = *p*-CF_3; 71%
2s, R = *p*-OCF_3; 68%
2t, R = *p*-OCH_3; 70%
2u, R = *m*-NO_2; 20% (38%)[d]

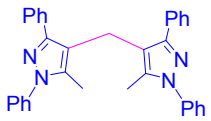


2v; 71%

2w; 70%



2x; traces (56%)[c]



2y; 22% (26%)[c]

[a]Reaction conditions: 1 (1 mmol), oxone (1 equiv) were stirred in DMSO (4 ml) at 150 °C for 2 h. [b]Isolated yields. [c]Reaction time 12 h. Yield of intermediate (methylthiomethylation) in parenthesis. [d]Reaction time 24 h. oxone (3 equiv). [e]Gram scale (4 g of reactant) reaction.

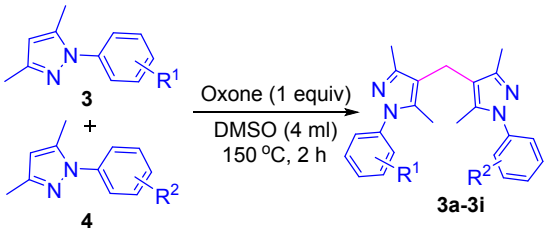
Notably, the yields of desired products were slightly higher in case of mono-*p*-halogen (-F, -Cl, -Br) substituted pyrazoles (**2d, 2g** and **2j**). The reaction of methyl and dimethyl substituted pyrazoles provide the targeted product in high yields (**2m-2p**). The reaction of pyrazole having trifluoromethyl and trifluoromethoxy groups, pharmaceutically important functional groups,[10] also undergone methylene insertion and gave product in good yields (**2q-2s**). Reaction of *p*-methoxy substituted pyrazole also provide the desired product in good yield (**2t**) and, *m*-nitro substituted compound gives the reaction intermediate under present conditions, however, on increasing the reaction time (24h) and quantity of oxidizing agent (3 equiv), both reaction intermediate (38%) and desired bis product (20%) were observed (**2u**). The reaction of pyrazole enclosing heteroaromatic (-2-pyridinyl) moiety also furnished the targeted product in reasonable yield (**2v**). Introduction of deuterium in a molecule with high yields is also demanding due to its prevalent applications in pharmaceutical fields[11] and DMSO-d_6 has been frequently used for this application.[11g] Herein, we envisioned that the reaction using DMSO-d_6 could have similar applications and it afforded the corresponding bis-pyrazole with two deuterium atoms in methylene moiety in good yield (**2w**). To expand the scope of the method, instead of dimethyl substituted pyrazoles, we have tried to explore other substitutions. Unfortunately, the reaction of 1,3,5-triphenyl-1*H*-pyrazole did not give desired product (trace of expected product appeared on TLC and LCMS) under present conditions even on increasing the reaction time, however, methylthiomethyl substituted intermediate was observed in moderate yield (**2x**) in this substrate. We assume that steric factor might be playing a role in this case. On decreasing the steric hindrance, *i.e.* in case of 5-methyl-1,3-diphenyl-1*H*-pyrazole (**2y**), desired product was observed in low yield along with its methylthiomethylated intermediate. Gram scale (4.0 g) reaction of the model substrate (1) afforded the corresponding bis-pyrazole in good yield (**2a,** 54%, 4.47 g),.

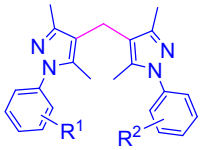
Furthermore, we have also investigated the scope of the present method for the synthesis of unsymmetric bis-pyrazoles executing the reactions with equivalent amounts of two different types of pyrazoles under optimal conditions (Table 3). The reactions of model substrate 1 (phenyl substituted pyrazole) with different halogens (-F, -Cl, -Br), methoxy and trifluoromethyl phenyl substituted pyrazoles, afforded the corresponding unsymmetric bis-pyrazoles as the major product in good to moderate yields (**3a-3d** and **3i**) along with two homo-dimers as symmetric bis-pyrazoles as minor products (see supporting information, Scheme S4). The methylene insertion reaction was also well supported in two pyrazoles with different substituents on phenyl rings providing unsymmetric bis-pyrazoles in good yields (**3e-3h**). On replacing phenyl ring of one pyrazole with heteroaromatic (-2-pyridinyl) ring also supported the formation of desired product (**3j**). The structure of **3j** was also confirmed using x-ray single crystal analysis (Table 3, **3j**). While carrying out control experiments, 4-methyl(thiomethyl) substituted pyrazole intermediate was isolated. In some earlier reports,[12,2p] DMSO has been decisively used for such transformations at various positions. The prologue of these types of thioethers is highly applicable as isosteres to alkenes, amides and ethers.[13] Herein, after cautious optimizations (provided in supporting information), we have revealed that another additive(y), KOAc, to the standard methylene insertion conditions, afforded the 4-methyl(thiomethyl) substituted pyrazoles in high yield (Scheme 2). Hence, we have explored the reactions for different pyrazoles providing corresponding 4-methyl(thiomethyl)pyrazoles in high yields (Scheme 2, **4a-4e**).

In literature,[6a] structurally similar to bis-pyrazoles, bis-imidazopyridine, having central carbonyl group, are known for their medicinal importance. Therefore, the synthesized symmetric as well as unsymmetric bis-pyrazole scaffolds were further exploited to the oxidized carbonyl compounds bearing bis-pyrazole scaffolds using TBHP as solvent and oxidant (Scheme 3, **5a** and **5b**). These carbonyl compounds were investigated for the reduction[14c-d] *via* simple sodium borohydride (Scheme 3, **5aa** and **5bb**) in high yields. Furthermore, these carbonyl compounds opens new area to

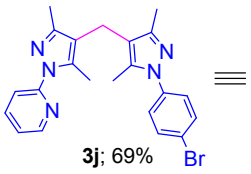
exploit for other organic transformations such as amination[14] etc. and two chiral centers can be easily generated in the complex molecule with very simple transformations (Scheme 3).

Table 3. Substrate scope for synthesis of unsymmetric bis-pyrazoles[a,b]

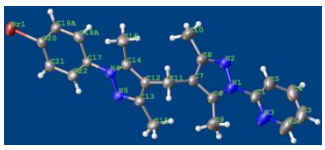




3a, R^1 = H, R^2 = *o*-Cl; 65%
3b, R^1 = H, R^2 = *p*-Cl; 68%
3c, R^1 = H, R^2 = *p*-Br; 70%
3d, R^1 = H, R^2 = *o*-CF_3; 40%
3e, R^1 = *m*-Cl, R^2 = *p*-Cl; 75%
3f, R^1 = *m*-Cl, R^2 = *m*-CF_3; 62%
3g, R^1 = *m*-Br, R^2 = *p*-OCH_3; 62%
3h, R^1 = *p*-Br, R^2 = *p*-OCH_3; 63%
3i, R^1 = H, R^2 = *p*-OCH_3; 67%



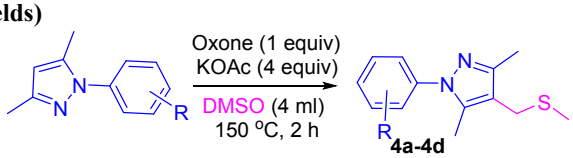
3j; 69%



crystal structure of **3j**[c]

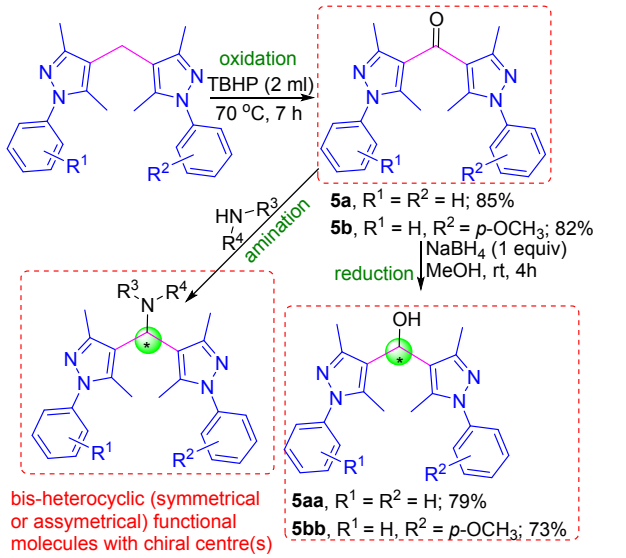
[a]Reaction conditions: 3 (1 mmol), 4 (1 mmol), oxone (1 equiv) were stirred in DMSO (4 ml) at 150 °C for 2 h. [b]Isolated yields. [c]X-ray crystallography analysis of compound 3j.

Scheme 2. Methyl thiomethylation of pyrazoles (Isolated yields)

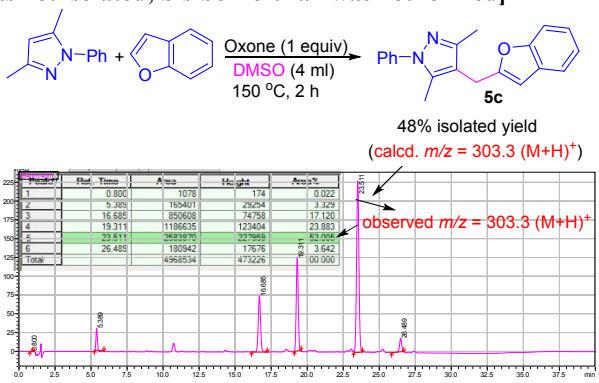


4a; R = H; 79% **4b**; R = *o*-CF_3; 70% **4c**; R = *m*-F; 73%
4d; R = *m*-CH_3; 82% **4e**; R = *m*-Cl, *p*-Cl; 69%

Scheme 3. Various important organic transformations with synthesized bis-pyrazoles



Scheme 4. Reaction of pyrazole with benzofuran [LC-MS (52%) characterization and isolated (48%) yields, homo-coupled bis-pyrazole also formed during the reaction but was not isolated; bis-benzofuran was not formed]

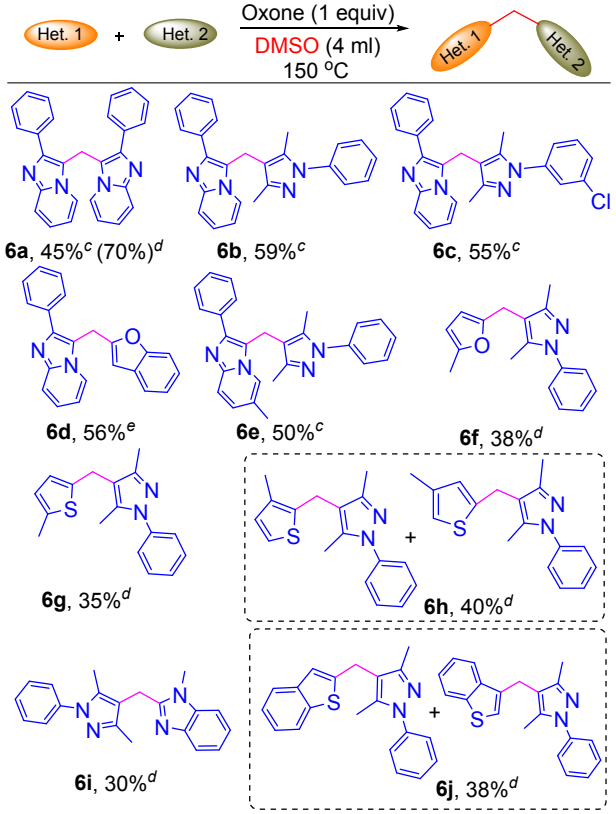


To explore the generality of the developed method, reactions for merging of two different type of heterocycles were examined. Reaction of 3,5-dimethyl-1-phenyl-1*H*-pyrazole with benzofuran afforded the desired product (**5c**) in fair yield (Scheme 4). Furthermore, reactions of different heterocycles afforded the hetero coupled heterocycles as the major product, although required longer reaction time even for moderate yields (Table 4). Reaction of 2-phenylimidazopyridine afforded the reaction intermediate, 3-((methylthio)methyl)-2-phenylimidazo[1,2-a]pyridine in 6 h in good yield and on increasing the reaction time to 24 h, symmetric bis-heterocyclic scaffold was obtained in moderate yield (**6a**). Reaction of 2-phenylimidazopyridine with other heterocyclic systems such as 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**6b**), 3,5-dimethyl-1-(3-chlorophenyl)-1*H*-pyrazole (**6c**) and benzofuran (**6d**) afforded the desired hetero coupled heterocyclic scaffolds in moderate yields. 6-methyl-2-phenylimidazopyridine also coupled with 3,5-dimethyl-1-phenyl-1*H*-pyrazole in moderate yield (**6e**). Reaction of 3,5-dimethyl-1-phenyl-1*H*-pyrazole with 2-methylfuran and 2-methylthiophene gave the hetero coupled heterocyclic scaffolds in low yields (**6f** and **6g**). The reaction of 3,5-dimethyl-1-phenyl-1*H*-pyrazole with 3-methylthiophene gave the mixture (at *o* and *o'* positions) of desired hetero coupled products (**6h**). Similarly, in case of reaction of 3,5-dimethyl-1-

phenyl-1*H*-pyrazole with benzothiophene, hetero coupled mixture of products (at 2 and 3 positions) were obtained (**6j**). Reaction of 1-methylbenzimidazole with 3,5-dimethyl-1-phenyl-1*H*-pyrazole provide the desired bis heterocyclic scaffold in low yield (**6i**).

To shed some light on the mechanism of the reaction, some control experiments (Scheme 5), mass analysis and DFT calculations were performed on the model reaction. Firstly, the deuterium labeling experiment confirmed the incorporation of methylene from the DMSO. One of the proposed intermediate (**10**) was isolated and, successfully, its reactions were carried out under standard conditions with two different pyrazole scaffolds for the synthesis of symmetric as well as unsymmetric bis-pyrazoles, confirming the possibility of formation of this intermediate in the proposed route. The LCMS study was also carried out by collecting the aliquots at different time intervals (45 min, 60 min, 90 min and 120 min) for mass comparisons (Figure S1). As perceived from the mass spectrum, intermediate **10D** is appearing at 45, 60 and 90 min. The reactant **1** is decreased as time progresses and formation of product **2** increases. This clearly supports the predicted route for formation of desired product (**2**).

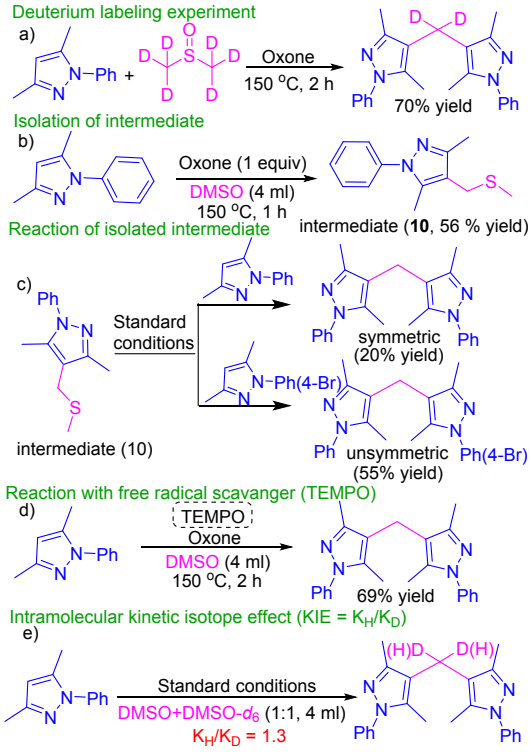
Table 4. Substrate scope for synthesis of bis-heterocycles[a,b,f]



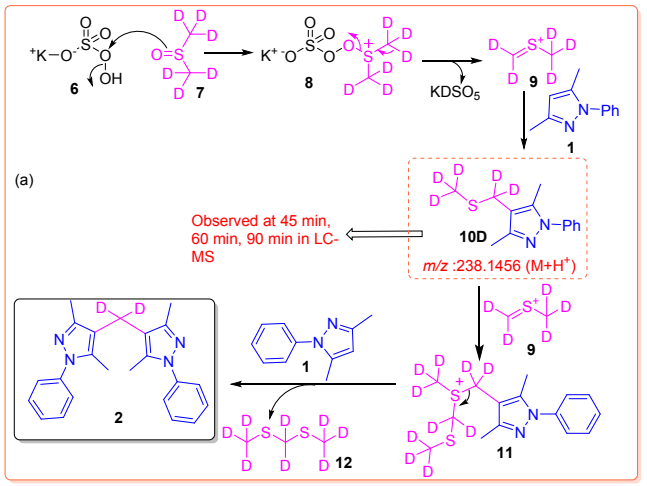
[a]Reaction conditions: Het. 1 (0.515 mmol), Het. 2 (0.515 mmol), oxone (0.515 mmol) were stirred in DMSO (4 ml) at 150 °C for 2 h. [b]Isolated yields, Yield of intermediate (methylthiomethylation) in parenthesis. [c]Reaction time 24 h. [d]Reaction time 6 h. [e]Reaction time 26 h. [f]homo-coupled bis-pyrazoles and bis-phenylimidazopyridines also formed in minor amount (based on TLC pattern) where pyrazole and phenylimidazopyridine scaffolds were used during the reaction but not isolated; other homo-coupled bis-heterocycles were not formed.

Reactions in the presence of free radical scavenger (TEMPO) afforded the desired product in good yield, ruling out the possibility of free radical pathway[4b] for the present method. The intramolecular kinetic isotope effect (KIE, KH/KD) of the methyl in DMSO was calculated and found to be 1.3. It indicated that the cleavage of C–H bond of DMSO is not the rate-determining step in the present reaction (Scheme 5). Further confirmation of the proposed plausible pathway (Scheme 6) was carried out using DFT studies (Scheme S10). The quantum chemical study revealed that the overall reaction is exothermic by 59.1 kcal/mol, thus indicating the thermodynamic feasibility of the reaction. Long-lived triplet state cation,[15] thionium ion intermediate **I** (or 9),[2r,16] is generated from DMSO and oxone by 136.9 kcal/mol of energy. Intermediate **I** reacts with **1** to form **III** via de-protonation of **II** and this process is exothermic by 169.4 kcal/mol. The reaction of **III** with **I** leading to the formation of **IV**[16b] is exothermic by 26.0 kcal/mol and further results into dithiopentane (**12**)[16b] as the side product. The C–C bond formation via TS along this pathway requires activation energy of 7.8 kcal/mol. Spontaneous de-protonation of **VI** in presence of KOH and HSO_5^- results into the final product **2** by releasing 138.3 kcal/mol energy.

Scheme 5. Control (a-d) and KIE (e) experiments



Scheme 6. Plausible reaction pathway



CONCLUSION

In conclusion, we have reported a novel method for the activation of DMSO towards methylene insertion in pyrazoles for the synthesis of bis-pyrazole scaffold via formation of new C—C bonds. We describe the dual role of DMSO as 'methylene source' and 'solvent' for the present reaction. We also extended the current method for synthesis of methylthiomethylated pyrazoles, oxidized bis-pyrazoles and incorporation of chiral centers in the bis-pyrazole scaffolds. Present protocol tolerated the variety of functional groups and afforded the symmetric as well as unsymmetric bis-pyrazoles in reasonably good yields. The mechanism of the current method was well established with the help of experimental, analytical (LC-MS) and computational (DFT) analysis.

EXPERIMENTAL SECTION

General Experimental. All solvents were purified and dried as per standard protocols. All reagents were obtained from commercial sources and used without purification. ^{1}H and ^{13}C NMR spectra were recorded on Brucker-Avance DPX FT-NMR 400 and 500 MHz instruments. ^{1}H and ^{13}C positive chemical shifts (δ) are downfield from tetramethylsilane and are given in parts per million (ppm). Multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, coupling constant(s) in Hz, integration). The HRMS spectra were recorded on Agilent 6540 Ultra-High-Definition (UHD) Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) liquid chromatography/mass spectrometry (LC/MS) system.

Computational Studies. All DFT studies[17] were performed using Gaussian09 suite software package.[18] The geometry optimization of all structures and transition state was carried out without any symmetry constraints using B3LYP method and 6-311+G(d,p) basis set.[19] Frequencies were calculated at the same level to confirm the nature of the stationary points of all geometries and transition state. Transition state was characterized by single imaginary frequency.

X-ray Crystal Structure Determination Studies of 3j. Single crystals of $C_{22}H_{22}BrN_5$ [sub-kas-csir, 3j] were prepared by slow evaporation. A suitable crystal was selected on a SuperNova, single source at offset/far, HyPix3000 diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2,[20] the structure was solved with the SIR2004[21] structure solution program using direct methods and refined with the ShelXL[22] refinement package using Least Squares minimization.

General Procedure for Synthesis of Pyrazole Starting Materials. Pyrazole starting materials were prepared according to our earlier report[9] (Scheme S1A).

Synthesis of 1,3,5-Triphenyl-1*H*-pyrazole. 1,3,5-triphenyl-1*H*-pyrazole was prepared according to earlier reports[23] (Scheme S1B).

General Procedure for Synthesis of Symmetric Bis-pyrazoles. A dry round bottom flask (25 ml) was charged with pyrazole (100 mg, 0.581 mmol), oxone® (356 mg, 0.581mmol)) in DMSO (4 ml) at 150 °C in oil-bath for 2 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired symmetric bis-product (Scheme S2).

Bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methane (2a) Light yellow liquid, yield = 71% (146 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.36 (m, 8H), 7.24–7.28 (m, 2H), 3.50 (s, 2H), 2.12 (s, 12H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 141.1, 136.2, 130.2, 130.1, 127.8, 123.1, 122.5, 116.1, 18.4, 12.3, 11.1 ppm. HRMS (ESI) Calcd for $C_{23}H_{25}N_4$ $[M+H]^+$ 357.2074; found 357.2055.

Bis(1-(2-fluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2b). Light yellow solid, m.p. 122-124 °C, yield = 64% (132 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.32 (m, 4H), 7.25-7.15 (m, 4H), 3.56 (s, 2H), 2.16 (s, 6H), 2.03 (d, *J* = 1.0 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9 (d, *J* = 251.1 Hz), 148.8, 138.2, 129.8 (d, *J* = 7.8 Hz), 127.9 (d, *J* = 12.1 Hz), 124.6 (d, *J* = 3.9 Hz), 116.4 (d, *J* = 20.2 Hz), 114.8, 18.5, 12.2, 9.8 (d, *J* = 4.0 Hz).^{19}F NMR (400 MHz, $CDCl_3$) δ -121.2 – -122.3 (m) ppm. HRMS (ESI) Calcd for $C_{23}H_{23}F_2N_4$ $[M+H]^+$ 393.1885; found 393.1863.

Bis(1-(3-fluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2c). Light yellow solid, m.p. 76-78 °C, yield = 66% (136mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37(m, 2H), 7.22-7.16 (m, 4H), 7.05-7.01 (m, 2H), 3.56 (s, 2H), 2.23 (s, 6H), 2.18 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8 (d, J = 247.2 Hz), 148.5, 141.4 (d, J = 9.9 Hz), 136.2, 130.2 (d, J = 9.2 Hz), 120.16 (d, J = 3.2 Hz), 116.17 (s), 114.04 (d, J = 21.1 Hz), 112.2 (d, J = 24.2 Hz), 18.5, 12.3, 11.2. 19F NMR (400 MHz, $CDCl_3$) δ -111.40 – -111.47 (m) ppm. HRMS (ESI) Calcd for $C_{23}H_{23}F_2N_4$ $[M+H]^+$ 393.1885; found 393.1883.

Bis(1-(4-fluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2d). Light yellow solid, m.p. 132-134 °C, yield = 69% (142mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 4H), 7.10 (t, *J* =16 Hz, 4H), 3.53 (s, 2H), 2.15 (s, 6H), 2.13 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (d, J = 247.1 Hz), 148.0, 136.3, 136.2 (d, J = 2.6 Hz), 126.8 (d, J = 8.6 Hz), 116.0, 115.7 (d, J = 18.8 Hz), 18.5, 12.3, 10.9.^{19}F NMR (400 MHz, $CDCl_3$) δ -114.43 – -114.43 (m) ppm. HRMS (ESI) Calcd for $C_{23}H_{23}F_2N_4$ $[M+H]^+$ 393.1885; found 393.1856.

Bis(1-(2-chlorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2e). Pale yellow liquid, yield = 65% (134mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 2H), 7.39-7.34 (m, 6H), 3.57 (s, 2H), 2.17 (s, 6H), 1.98 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ

148.4, 138.1, 137.7, 132.7, 130.2 ,130.1, 127.6, 114.5, 18.5, 12.4, 10.0 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Cl_2N_4$ $[M+H]^+$ 425.1294; found 425.1284.

Bis(1-(3-chlorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2f). Pale yellow semi-solid, yield = 65% (134 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 1.9 Hz, 2H), 7.35 (dd, *J* = 8.6, 7.1 Hz, 2H), 7.31-7.26 (m, 4H), 3.54 (s, 2H), 2.20 (s, 6H), 2.16 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.5, 141.0, 136.3, 134.7, 130.0, 127.2, 125.0, 122.7, 116.1, 18.5, 12.3, 11.2 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Cl_2N_4$ $[M+H]^+$ 425.1294; found: 425.1270.

Bis(1-(4-chlorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2g). Brown solid, m.p. 142-144 °C, yield = 78% (160 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 4H), 7.35-7.31 (m, 4H), 3.54 (s, 2H), 2.17 (s, 6H), 2.16 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.4, 138.5, 136.3, 132.9, 129.2, 126.0, 116.0, 18.5, 12.3, 11.1 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Cl_2N_4$ $[M+H]^+$ 425.1294; found 425.1290.

Bis(1-(2-bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2h). Yellow liquid, yield = 63% (129 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.41-7.33 (m, 4H), 7.30-7.25 (m, 2H), 3.57 (s, 2H), 2.18 (s, 6H), 1.98 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.2, 139.4, 137.9, 133.3, 130.4, 130.2, 128.2, 122.8, 114.6, 18.5, 12.4, 10.2 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Br_2N_4$ $[M+H]^+$ 513.0284; found 513.0254.

Bis(1-(3-bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2i). White solid, m.p. 168-170 °C, yield = 68% (139 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, *J* = 1.9 Hz, 2H), 7.45-7.43 (m, 2H), 7.34-7.28 (m, 4H), 3.53 (s, 2H), 2.19 (s, 6H), 2.15 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.5, 141.1, 136.3,130.2, 130.1,127.8, 123.1, 122.5, 116.1, 18.4, 12.3, 11.2 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Br_2N_4$ $[M+H]^+$ 513.0284; found 513.0281.

Bis(1-(4-bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2j). White solid, m.p. 170-172 °C, yield = 80% (164 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 4H), 7.27 (d, *J* = 8.6 Hz, 4H), 3.53 (s, 2H), 2.17 (s, 6H), 2.15 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.3, 139.0, 136.1, 132.1, 126.2, 120.7, 116.0, 18.5, 12.3, 11.1 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Br_2N_4$ $[M+H]^+$ 513.0284; found 513.0273.

Bis(1-(2,4-difluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2k). Light yellow solid, m.p. 136-138 °C, yield = 61% (125mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 2H), 6.96-6.88 (m, 4H), 3.53 (s, 2H), 2.12 (s, 6H), 1.98 (d, *J* = 4 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3 (dd, *J* = 251.0,11.1 Hz),159.8 (dd, *J* = 265.6,11.1 Hz), 157.2 (dd = 255.5, 17.1 Hz), 149.1, 138.4, 130.2 (dd, *J* = 10.1, 1.0 Hz), 124.3 (dd, *J* = 12.1, 4.0 Hz), 115.1, 111.8 (dd, *J* = 23.2, 4.0 Hz), 105.1, 104.7 (d, *J* = 3.0 Hz),104.6, 18.6, 12.35, 9.9 (d, *J* = 3.0 Hz) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -108.39 – -108.42 (m),-117.02 – -117.09 (m) ppm. HRMS (ESI) Calcd for $C_{23}H_{21}F_4N_4$ $[M+H]+$ 429.1697; found 429.1688.

Bis(1-(2,4-dichlorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2l). Light yellow solid, m.p. 132-134 °C, yield = 63% (129mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR$\{^1H\}$ (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 1.9 Hz, 2H), 7.33-7.29 (m, 4H), 3.56 (s, 2H), 2.15 (s, 6H), 1.97 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.8, 138.2, 136.4, 135.5, 133.5, 130.9, 130.1, 128.0, 114.8, 18.5, 12.3, 10.0 ppm. HRMS (ESI) Calcd for $C_{23}H_{21}Cl_4N_4$ $[M+H]+$ 493.0515; found 493.0491.

Bis(3,5-dimethyl-1-(o-tolyl)-1*H*-pyrazol-4-yl)methane (2m). White solid, m.p. 75-76 °C, yield = 72% (148 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.20 (m, 6H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.57 (s, 2H), 2.15 (s, 6H), 2.00 (s, 6H), 1.92 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.4, 138.9, 137.1, 136.3, 130.8, 128.9, 128.1, 126.5, 114.2, 18.5, 17.2, 12.3, 10.0 ppm. HRMS (ESI) Calcd for $C_{25}H_{29}N_4$ $[M+H]^+$ 385.2387; found 385.2360.

Bis(3,5-dimethyl-1-(m-tolyl)-1*H*-pyrazol-4-yl)methane (2n). Yellow liquid, yield = 73% (150 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 8.4 Hz , 4H), 3.47 (s, 2H), 2.30 (s, 6H), 2.10 (s, 6H), 2.09 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.8, 140.0, 139.1, 136.2, 128.7, 128.0, 125.7, 121.9, 115.6, 21.3, 18.6, 12.3, 11.1 ppm. HRMS (ESI) Calcd for $C_{25}H_{29}N_4$ $[M+H]^+$ 385.2387; found 385.2359.

Bis(3,5-dimethyl-1-(p-tolyl)-1*H*-pyrazol-4-yl)methane (2o). Light yellow solid, m.p. 158-160 °C, yield = 74% (152 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.20 (m, 4H), 7.18 (m, 4H), 3.51 (s, 2H), 2.34 (s, 6H), 2.13 (s, 6H), 2.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.7, 137.7, 137.2, 136.3, 129.6, 125.0, 115.5, 21.1, 18.6, 12.3, 11.0 ppm. HRMS (ESI) Calcd for $C_{25}H_{29}N_4$ $[M+H]^+$ 385.2387; found 385.2365.

Bis(1-(3,4-dimethylphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2p). Yellow liquid, yield = 76% (156 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 9.5, 5.0 Hz, 4H), 7.07 (dd, *J* = 8.0, 2.2 Hz, 2H), 3.55 (s, 2H), 2.28 (s, 12H), 2.18 (s, 6H), 2.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.5, 137.9, 137.5, 136.2, 135.7, 129.9, 126.3, 122.3, 115.3, 19.8, 19.4, 18.6, 12.3, 11.0 ppm. HRMS (ESI) Calcd for $C_{27}H_{33}N_4$ $[M+H]^+$ 413.2700; found 413.2687.

Bis(3,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)methane (2q). Pale yellow liquid, yield = 71% (145 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.60-7.54 (m, 6H), 3.56 (s, 2H), 2.22 (s, 6H), 2.17 (s, 6H) ppm. ^{13}C NMR$\{^1H\}$(101 MHz, $CDCl_3$) $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.6, 144.2, 140.0, 135.4 (q, *J* = 32.8 Hz), 133.4, 131.4, 128.8, 127.5 (q, *J* = 3.8 Hz), 126.1, 125.3 (q, *J* = 3.9 Hz), 120.1, 22.2, 16.1, 14.9 ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.6 (s) ppm. HRMS (ESI) Calcd for $C_{25}H_{23}F_6N_4$ $[M+H]^+$ 493.1821; found 493.1824.

Bis(3,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)methane (2r). White solid, m.p. 127-129 °C, yield = 71% (145 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.0 Hz, 4H), 7.56 (d, *J* = 2.0 Hz, 4H), 3.58 (s, 2H), 2.26 (s, 6H), 2.18 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 142.9, 136.3, 128.9 (d, *J* = 32.7 Hz), 126.3 (q, *J* = 3.7 Hz), 125.5 (d, *J* = 27.2 Hz), 124.4, 122.5, 116.6, 18.6, 12.4, 11.4ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.3 (s) ppm. HRMS (ESI) Calcd for $C_{25}H_{23}F_6N_4$ $[M+H]^+$ 493.1821; found 493.1827.

Bis(3,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-4-yl)methane (2s). Pale yellow solid, m.p. 108-110 °C, yield = 68% (139 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.37 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 4H), 3.54 (s, 2H), 2.18 (s, 6H), 2.15 (s, 6H) ppm. $^{13}C\{^1H\}$

NMR (101 MHz, $CDCl_3$) δ 148.5, 147.9 (d, *J* = 1.7 Hz), 138.6, 136.3, 126.1, 121.7 (d, *J* = 8.6 Hz), 119.2, 116.0, 18.5, 12.3, 11.1ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -58.0 (s) ppm. HRMS (ESI) Calcd for $C_{25}H_{23}F_6N_4O_2$ $[M+H]^+$ 525.1720; found 525.1724.

Bis(1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methane (2t). Light brown solid, m.p. 158-160 °C, yield = 70% (144 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 6.65-6.61 (m, 4H), 6.29 (d, *J* = 8.9 Hz, 4H), 3.17 (s, 6H), 2.89 (s, 2H), 1.52 (s, 6H), 1.46 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8, 147.4, 136.4, 133.2, 126.6, 115.2, 114.2, 55.6, 18.6, 12.3, 10.8 ppm. HRMS (ESI) Calcd for $C_{25}H_{29}N_4O_2$ $[M+H]^+$ 417.2285; found 417.2279.

Bis(3,5-dimethyl-1-(3-nitrophenyl)-1*H*-pyrazol-4-yl)methane (2u). *Bis-pyrazole.* Colourless liquid, yield = 20% (41 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 2H), 8.20 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.1 Hz, 2H), 3.61 (s, 2H), 2.31 (s, 6H), 2.21 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.3, 148.6, 140.9, 136.3, 129.9 (d, J = 2.7 Hz), 121.5, 119.0, 116.7, 18.4, 12.3, 11.3. HRMS (ESI) Calcd for $C_{23}H_{23}N_6O_4$ $[M+H]^+$ 447.1775; found 447.1779.

3,5-dimethyl-4-((methylthio)methyl)-1-(3-nitrophenyl)-1*H*-pyrazole (Intermediate). Colourless liquid, yield = 38% (48 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ δ 8.32 (m, 1H), 8.18 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.63 (t, *J* = 8.1 Hz, 1H), 3.57 (s, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 2.09 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.7, 148.5, 140.8, 137.4, 130.0, 129.8, 121.5, 119.0, 115.7, 27.0, 15.3, 11.9, 11.3 ppm. HRMS (ESI) Calcd for $C_{13}H_{16}N_3O_2S$ $[M+H]^+$ 278.0958; found 278.0960

Bis(3,5-dimethyl-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methane (2v). White solid, m.p. 115-118 °C, yield = 71% (146 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 8.44-8.40 (m, 1H), 7.81-7.76 (m, 2H), 7.15-7.12 (m, 2H), 3.58 (s, 2H), 2.59 (s, 6H), 2.18 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 149.2, 147.5, 138.2, 137.9, 120.7, 117.2, 116.2, 18.0, 12.6 ppm. HRMS (ESI) Calcd for $C_{21}H_{23}N_6$ $[M+H]^+$ 359.1979; found 359.1982.

Bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methane-d2 (2w). Pale yellow solid, m.p. 120-122 °C, yield = 70% (145 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.36 (m, 8H), 7.33-7.29 (m, 2H), 2.18 (d, *J* = 1.5 Hz,12H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.9, 140.0 ,136.2, 128.9, 127.1, 124.9, 115.5, 12.2, 11.0 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}D_2N_4$ $[M+H]^+$ 359.2199; found 359.2201.

4-((methylthio)methyl)-1,3,5-triphenyl-1*H*-pyrazole (intermediate) (2x). Orange liquid, yield = 56%(67mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.45-7.41 (m, 6H), 7.36-7.25 (m, 5H), 3.73 (s, 2H), 2.05 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.5, 142.4, 139.9, 133.3, 130.1, 128.7, 128.6, 128.5, 128.2, 128.0, 127.0, 124.8, 115.3, 28.4, 16.3 ppm. HRMS (ESI) Calcd for $C_{23}H_{21}N_2S$ $[M+H]^+$ 357.1420; found 357.1408.

Bis(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)methane (2y). Brown viscous, yield = 22%(45 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.2 Hz, 6H), 7.14 (d, *J* = 7.6 Hz, 4H), 7.08 (m, 6H), 6.95 (m, 4H), 3.62 (s, 2H), 1.99 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.5, 140.6, 140.1, 130.8, 130.1, 128.6, 128.3, 128.1, 126.4, 124.5, 117.1, 18.6, 12.4 ppm. HRMS (ESI) Calcd for $C_{33}H_{29}N_4$ $[M+H]^+$ 481.2387; found 481.2361.

3-methyl-4-((methylthio)methyl)-1,5-diphenyl-1*H*-pyrazol e (Intermediate).Colourless liquid, yield = 26%(125 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.27 (m, 3H), 7.24 (s, 1H), 7.20 (m, 3H), 3.58 (s, 2H), 2.44 (s, 3H), 2.01 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.0, 141.4, 139.9, 130.3, 129.9, 128.7, 128.5, 128.3, 126.7, 124.6, 115.6, 27.3, 15.7, 12.1 ppm. HRMS (ESI) Calcd for $C_{18}H_{19}N_2S$ $[M+H]^+$ 295.1263; found 295.1260.

General Procedure for Synthesis of Unsymmetric Bis-pyrazoles. A dry round bottom flask (25 ml) was charged with pyrazole 1 (100 mg, 0.581 mmol), pyrazole 2 (119 mg, 0.581 mmol)), oxone (357 mg, 0.581 mmol) in DMSO (4 ml) at 150 °C in oil-bath for 2 h (3a). After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired unsymmetric bis-product (Scheme S3).

1-(2-chlorophenyl)-4-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3a). Light yellow solid, m.p. 94-95 °C, yield = 65% (147 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 1H), 7.46-7.30 (m, 8H), 3.59 (s, 2H), 2.20 (s, 3H), 2.19 (d, *J* = 2.9 Hz, 6H), 2.00 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.2, 147.9, 140.0, 137.9, 137.6, 136.2, 132.5, 130.1, 130.0, 128.9, 127.5, 127.1, 124.8, 115.5, 114.5, 18.4, 12.3, 12.2, 10.9, 9.9 ppm. HRMS (ESI) Calcd for $C_{23}H_{24}ClN_4$ $[M+H]^+$ 391.1684; found 391.1666.

1-(4-chlorophenyl)-4-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3b). Yellow semi-solid, yield = 68% (154 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.37 (m, 6H), 7.36-7.30 (m, 3H), 3.56 (s, 2H), 2.18 (d, *J* = 2.7 Hz, 12H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.4, 147.9, 140.1, 138.7, 136.3, 132.9, 129.2, 129.1, 127.3, 126.0, 125.0, 116.2, 115.5, 18.6, 12.4, 12.3, 11.1 ppm. HRMS (ESI) Calcd for $C_{23}H_{24}ClN_4$ $[M+H]^+$ 391.1684; found 391.1671.

1-(4-bromophenyl)-4-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3c). White viscous, yield = 70% (177 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.46-7.39 (m, 4H), 7.32 (m, 3H), 3.56 (s, 2H), 2.19 (d, *J* = 4.0 Hz, 12H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.4, 147.9, 140.0, 139.1, 136.2,132.1, 129.0, 127.3, 126.2, 124.9, 120.7, 116.2, 115.5, 18.5, 12.3, 11.1 (d, *J* = 4.0 Hz) ppm. HRMS (ESI) Calcd for $C_{23}H_{24}BrN_4$ $[M+H]^+$ 435.1179; found 435.1187.

4-((3,5-dimethyl-1-(2-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (3d). Light brown semi-solid, yield = 40% (106 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.0 Hz, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45-7.38 (m, 4H), 7.35-7.30 (m, 2H), 3.57 (s, 2H), 2.19 (s, 3H), 2.15 (d, *J* = 4.5 Hz, 6H), 1.91 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.1, 140.2, 138.3, 138.0, 136.4, 132.7, 130.9, 129.5, 129.1, 127.3 (d, *J* = 5.0 Hz), 127.3, 125.1, 115.6, 114.6, 18.6, 12.3, 12.2, 10.9, 10.1 ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -60.34 (s) ppm. HRMS (ESI) Calcd for $C_{24}H_{24}F_3N_4$ $[M+H]^+$ 425.1948; found 425.1948.

1-(3-chlorophenyl)-4-((1-(4-chlorophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3e). Dark brown semi-solid, yield = 75% (165 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37-7.34 (m, 2H), 7.32 (s, 2H), 7.27-7.24 (m, 3H), 3.52 (s, 2H), 2.18 (s, 3H), 2.14 (m, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.4, 148.2, 140.9, 138.4, 136.17, 134.6, 132.7, 129.9, 129.0, 127.1, 125.8, 124.8, 122.5, 116.0, 116.0, 115.8, 115.8, 18.3, 12.2, 11.1, 11.0 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}Cl_2N_4$ $[M+H]^+$ 425.1294; found 425.1294.

1-(3-chlorophenyl)-4-((3,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3f). Yellow oil, yield = 62% (138 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.62-7.56(m, 3H), 7.45 (s, 1H), 7.38-7.29 (m, 3H), 3.56 (t, *J* = 3.0 Hz, 2H), 2.22 (q, *J* = 1.0 Hz, 6H), 2.18 (q, *J* = 1.0 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.6, 141.1, 140.5, 136.3, 134.8, 132.0, 131.6, 130.0, 129.7, 127.7, 127.3, 125.1, 123.8, 122.8, 121.6 (q, *J* = 4.0 Hz), 116.4 (d, *J* = 7.0 Hz), 116.1 (d, *J* =7.0 Hz), 18.6, 12.4, 11.2 ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.68 (s) ppm. HRMS (ESI) Calcd for $C_{24}H_{22}ClF_3N_4$ $[M+H]^+$ 459.1558; found 459.1561.

1-(3-bromophenyl)-4-((1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3g). Light brown solid, m.p. 142-144 °C, yield = 62% (115 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.34-7.30 (m, 2H), 7.28-7.23 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 3.53 (s, 2H), 2.17-2.14 (m, 9H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.8, 148.4, 147.3, 138.6, 136.4, 136.2, 133.2, 132.8, 129.1, 126.5, 125.9, 116.2, 114.9, 114.2, 55.5, 18.5, 12.2, 11.1, 10.8 ppm. HRMS (ESI) Calcd for $C_{24}H_{26}BrN_4O$ $[M+H]^+$ 465.1285; found 465.1290.

1-(4-bromophenyl)-4-((1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazole (3h). Light yellow solid, m.p. 168-170 °C, yield = 63% (117 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.31-7.29 (m, 4H), 6.97-6.94 (m, 2H), 3.84 (s, 3H), 3.56 (s, 2H), 2.20-2.18 (m, 9H), 2.13 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.8, 148.5, 147.4, 139.15, 136.41, 136.1, 133.2, 132.1, 126.5, 126.2, 120.6, 116.3, 114.9, 114.2, 55.5, 18.5, 12.2, 11.1, 10.8 ppm. HRMS (ESI) Calcd for $C_{24}H_{26}BrN_4O$ $[M+H]^+$ 465.1285; found 465.1268.

4-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazole (3i). Light yellow viscus, yield = 67% (150 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.57 (s, 2H), 2.19 (s, 9H), 2.13 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.8, 147.9, 147.3, 136.4, 136.2, 129.0, 127.2, 126.5, 124.9, 115.7, 115.0, 114.1, 55.5, 18.5, 12.2, 11.0, 10.8 ppm. HRMS (ESI) Calcd for $C_{24}H_{27}N_4O$ $[M+H]^+$ 387.2179; found 387.2169.

2-(4-((1-(4-bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methyl)-3,5-dimethyl-1*H*-pyrazol-1-yl)pyridine (3j). White solid, m.p. 140-142 °C, yield = 69% (173 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.40 (m, 1H), 7.79 (m, 2H), 7.60-7.54 (m, 2H), 7.34-7.27 (m, 2H), 7.17-7.14 (m, 1H), 3.58 (s, 2H), 2.59 (s, 3H), 2.20 (s, 3H), 2.18 (d, *J* = 2.3 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.6, 149.1, 148.4, 147.4, 139.0, 138.1, 137.8, 136.2, 132.1, 126.2 , 120.7, 117.1, 116.1, 116.0, 18.2, 12.6, 12.5, 12.2, 11.0 ppm. HRMS (ESI) Calcd for $C_{22}H_{23}BrN_5$ $[M+H]^+$ 436.1131; found 436.1136.

General Procedure for Methyl Thiomethylation of Pyrazoles. A dry round bottom flask (25 ml) was charged with pyrazole (100 mg, 0.581 mmol), oxone (357 mg,0.581 mmol), KOAc (57 mg, 0.581 mmol) in DMSO (4 ml) at 150 °C in oil- bath for 2 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired product (Scheme S5).

3,5-dimethyl-4-((methylthio)methyl)-1-phenyl-1*H*-pyrazole (4a). Colourless liquid, yield = 79% (106 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 4H), 7.38-7.34 (m,1H), 3.60 (s, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.2, 139.8, 137.3, 129.0, 127.3, 124.8, 114.1, 27.1, 15.2, 11.9, 11.0 ppm. HRMS (ESI) Calcd for $C_{13}H_{17}N_2S$ $[M+H]^+$ 233.1107; found 233.1101.

3,5-dimethyl-4-((methylthio)methyl)-1-(2-(trifluoromethyl)phenyl)-1*H*-pyrazole (4b). Colourless liquid, yield = 70% (86 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 3.55 (s, 2H), 2.28 (s, 3H), 2.03-1.99 (m, 6H) ppm. ^{13}C NMR{^{1}H}(101 MHz, $CDCl_3$) δ 148.3, 139.3, 137.5, 132.6, 130.6, 129.5, 128.5 (d, *J* = 31.4 Hz), 127.2 (q, *J* = 4.9 Hz), 123.9, 121.7, 112.8, 26.7, 14.5, 11.8, 9.9 ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -60.50 (s) ppm. HRMS (ESI) Calcd for $C_{14}H_{16}F_3N_2S$ $[M+H]^+$ 301.0981; found 301.0981.

1-(3-fluorophenyl)-3,5-dimethyl-4-((methylthio)methyl)-1*H*-pyrazole (4c). Colourless liquid, yield = 73% (96 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 1H), 7.25-7.22 (m, 2H), 7.09-7.04 (m, 1H), 3.58 (s, 2H), 2.33 (d, *J* = 3.5 Hz, 6H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.2 Hz), 148.8, 141.1 (d, *J* = 10.1 Hz), 137.3, 130.2 (d, *J* = 9.1 Hz), 120.0 (d, *J* = 3.1 Hz), 114.7, 114.1 (d, *J* = 21.1 Hz), 112.0 (d, *J* = 24.4 Hz), 27.0, 15.2, 11.9, 11.19 ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -111.34 - (-111.41) ppm. HRMS (ESI) Calcd for $C_{13}H_{16}FN_2S$ $[M+H]^+$ 251.1013; found 251.1006.

3,5-dimethyl-4-((methylthio)methyl)-1-(m-tolyl)-1*H*-pyrazole (4d). Colourless liquid, yield = 82% (108 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.7 Hz, 1H), 7.27-7.24 (m, 1H), 7.16 (t, *J* = 7.0 Hz, 2H), 3.57 (s, 2H), 2.40 (s, 3H), 2.31 (d, *J* = 0.6 Hz, 3H), 2.28 (s, 3H), 2.08 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.1, 139.7, 139.2, 137.3, 128.7, 128.1, 125.6, 121.7, 113.9, 27.1, 21.3, 15.2, 11.9, 11.0 ppm. HRMS (ESI) Calcd for $C_{14}H_{19}N_2S$ $[M+H]^+$ 247.1263; found 247.1252.

1-(3,4-dichlorophenyl)-3,5-dimethyl-4-((methylthio)methyl)-1*H*-pyrazole (4e). Colourless liquid, yield = 69% (86 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.32-7.29 (m, 1H), 3.57 (s, 2H), 2.33 (d, *J* = 3.5 Hz, 6H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 139.1, 137.3, 133.0, 131.1, 130.6, 126.3, 123.4, 115.1, 27.0, 15.3, 11.8, 11.1 ppm. HRMS (ESI) Calcd for $C_{13}H_{15}Cl_2N_2S$ $[M+H]^+$ 301.0328; found 301.0309.

General Procedure for Oxidation of Bis-pyrazoles (Synthesis of 5a and 5b). A dry round bottom flask (25 ml) was charged with bis-pyrazole (100 mg, 0.280 mmol) in TBHP (2 ml) at 70 °C for 7 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired product (Scheme S6).

Bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (5a). Light yellow liquid, yield = 85% (88 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 4H), 7.43 (m, 6H), 2.36 (s, 6H), 2.31 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.7, 149.4, 141.9, 138.8, 129.2, 128.4, 125.4, 122.2, 13.1, 11.9 ppm. HRMS (ESI) Calcd for $C_{23}H_{23}N_4O$ $[M+H]^+$ 371.1866; found 371.1854.

(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)(1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methanone (5b). Colourless liquid, yield = 82% (85 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 5.9 Hz, 2H), 7.44 (s, 3H), 7.33 (d, *J* = 6.4 Hz, 2H), 6.99 (d, *J* = 6.3 Hz, 2H), 3.86 (d, *J* = 2.7 Hz, 3H), 2.37 (d, *J* = 2.7 Hz, 3H), 2.32 (m, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.7, 159.6, 149.3, 149.1, 142.1, 141.8, 138.8, 131.7, 129.2, 128.4, 126.9, 125.4, 122.2, 121.8, 114.4, 55.6, 13.1, 11.9, 11.8. HRMS (ESI) Calcd for $C_{24}H_{25}N_4O_2$ $[M+H]^+$ 401.1972; found 401.1947.

General Procedure for Reduction of 5a and 5b (Synthesis of 5aa and 5bb). A dry round bottom flask (25 ml) was charged with 5a or 5b (100 mg, 0.270 mmol.), $NaBH_4$ (10 mg, 0.270 mmol.) in methanol (4 ml) at rt for 4 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired product (Scheme S7).

Bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methanol (5aa). Colourless liquid, yield = 79% (79 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, MeOD) δ 6.65-6.61 (m, 4H), 6.57-6.49 (m, 6H), 5.08 (s, 1H), 1.35 (s, 6H), 1.28 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 147.1, 139.2, 137.6, 128.9, 127.9, 125.5, 118.8, 62.0, 11.2, 9.9 ppm. HRMS (ESI) Calcd for $C_{23}H_{25}N_4O$ $[M+H]^+$ 373.2023; found 373.2017.

(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)(1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methanol (5bb). Colourless liquid, yield = 73% (73 mg). R_f 0.6 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz,2H), 7.42 – 7.37 (m, 3H), 7.29 (d, *J* = 8.9 Hz,2H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.99 (s, 1H), 3.85 (s, 3H), 2.28 (s, 3H), 2.22 (d, *J* = 2.9 Hz, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.1, 147.2, 146.7, 139.6, 137.1, 136.8, 132.6, 129.0, 127.6, 126.9, 125.4, 118.6, 118.1, 114.2, 63.5, 55.5, 12.8, 12.8, 11.4, 11.2 ppm. HRMS (ESI) Calcd for $C_{24}H_{27}N_4O_2$ $[M+H]^+$ 403.2129; found 403.2119.

General Procedure for Synthesis of 5c. A dry round bottom flask (25 ml) was charged with pyrazole 1 (100 mg, 0.581 mmol), benzofuran (68 mg, 0.581 mmol), oxone (356 mg, 0.581 mmol) in DMSO (4 ml) at 150 °C in oil-bath for 2 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired product (Scheme S8).

4-(benzofuran-2-ylmethyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (5c). Colourless liquid, yield = 48% (84 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 6H), 7.37-7.33 (m, 1H), 7.26-7.16 (m,2H), 6.30 (s,1H), 3.91 (s, 2H), 2.30 (d, *J* = 4.3 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.5, 154.9, 148.2, 139.9, 137.2, 129.0, 128..8, 127.3, 124.8, 123.3, 122.5, 120.3, 113.1, 110.8, 102.4, 23.3, 11.9, 11.0 ppm. MS (ESI) Calcd for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492; found 303.1491.

bis(2-phenylimidazo[1,2-a]pyridin-3-yl)methane (6a). Light brown liquid, yield = 45% (92mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.3 Hz, 4H), 7.56–7.49 (m, 6H), 7.43 (t, *J* = 7.3 Hz,2H), 7.35 (d, *J* = 6.9 Hz, 2H), 7.09–7.02 (m, 2H), 6.48 (t, *J* = 6.8 Hz, 2H), 5.00 (s, 2H)ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.0, 144.1, 134.2, 128.9, 128.8, 128.2, 124.3, 123.7, 117.4, 114.3, 112.3, 19.7. HRMS (ESI) Calcd for $C_{27}H_{21}N_4$ $[M+H]^+$ 401.1761; found 401.1780.

3-((methylthio)methyl)-2-phenylimidazo[1,2-a]pyridine (6a). Yellow liquid, yield = 65 % (85 mg). R_f 0.5 (EtOAc:*n*-Hexane = 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.7 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.31–7.21 (m, 1H), 6.92 (t, *J* = 6.8 Hz, 1H), 4.24 (s, 2H), 2.02 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)δ 145.1, 144.8, 134.2, 128.6, 128.5, 127.8, 124.5, 124.1, 117.6, 115.2, 112.1, 27.3, 15.0 ppm. HRMS (ESI) Calcd for $C_{15}H_{15}N_2S$ $[M+H]^+$ 255.0950; found 255.0964.

3-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-2-phenylimidazo[1,2-a]pyridine (6b). Light brown liquid, yield = 59% (115 mg). R_f 0.4 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 3H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.42 – 7.36 (m, 3H), 7.32 (s, 3H), 7.20 (s, 1H), 6.78 (s, 1H), 4.31 (s, 2H), 2.08 (s, 3H), 1.85 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.6, 144.5, 139.6, 136.6, 134.6, 128.9, 128.6,128.5, 127.7, 127.4, 125.0, 124.0, 123.3, 117.6, 117.3, 112.3, 111.5, 19.7, 12.0, 10.4ppm. HRMS (ESI) Calcd for $C_{25}H_{23}N_4$ $[M+H]^+$ 379.1917; found 379.1933.

3-((1-(3-chlorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)methyl)-2-phenylimidazo[1,2-a]pyridine (6c). Light yellow liquid, yield = 55% (116 mg). R_f 0.3 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 6.3 Hz, 3H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.37 (dd, *J* = 7.7, 5.9 Hz,2H), 7.31 (dd, *J* = 12.1, 7.8 Hz, 2H), 7.21 (dd, *J* = 10.9, 3.6 Hz, 2H), 6.80 (t, *J* = 6.7 Hz,1H), 4.30 (s, 2H), 2.07 (s, 3H), 1.88 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.3, 144.4, 143.4, 140.5, 136.7, 134.7, 134.1, 130.0, 128.6, 128.0, 127.5, 125.2, 124.4, 123.3, 122.8, 117.5, 117.2, 112.6, 112.2, 19.6, 12.0, 10.5 ppm. HRMS (ESI) Calcd for $C_{25}H_{22}N_4Cl$ $[M+H]^+$ 413.1528; found 413.1536.

3-(benzofuran-2-ylmethyl)-2-phenylimidazo[1,2-a]pyridine (6d). Dark yellow liquid, yield = 56 % (93 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.9 Hz, 1H), 7.89–7.81 (m, 2H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.29–7.16 (m, 3H), 6.81 (t, *J* = 6.7 Hz, 1H), 6.35 (s, 1H), 4.56 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.5,

155.2, 146.4, 145.7, 135.5, 130.1, 129.8, 129.3, 125.9, 125.4, 124.8, 124.3, 122.1, 119.1, 116.1, 113.8, 112.4, 105.1, 25.7 ppm. HRMS (ESI) Calcd for $C_{22}H_{17}N_2O$ $[M+H]^+$ 325.1335; found 325.1349.

3-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-6-methyl-2-phenylimidazo[1,2-a]pyridine (6e). Light yellow liquid, yield = 50 % (94 mg). R_f 0.5 (EtOAc:*n*-Hexane = 3:7). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.77 (m, 2H), 7.61 – 7.56 (m, 2H), 7.49 – 7.41 (m, 4H), 7.39 – 7.32 (m, 4H), 7.08-7.05 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 1.88 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 145.1, 144.8, 141.0, 138.0, 136.3, 130.3, 129.9,129.9 128.9, 128.8, 128.4, 126.4, 123.2, 122.3, 118.4, 118.3, 113.2, 21.1, 19.9, 13.4, 11.8 ppm. HRMS (ESI) Calcd for $C_{26}H_{25}N_4$ $[M+H]^+$ 393.2074; found 393.2085.

3,5-dimethyl-4-((3-methylfuran-2-yl)methyl)-1-phenyl-1*H*-pyrazole (6f). Yellow liquid, yield = 38 % (58 mg). R_f 0.5 (EtOAc:*n*-Hexane = 0.5:9.5). ^1H NMR (400 MHz, $CDCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 4H), 7.34-7.31 (m, 1H), 5.83 (s, 1H), 5.77 (s, 1H), 3.70 (s, 2H), 2.25 (d, *J* = 4.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.5, 150.5, 147.8, 140.1, 137.1, 128.8, 127.1, 124.8, 114.5, 105.8, 22.8, 13.5, 11.9, 10.9 ppm. HRMS (ESI) Calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1492; found 267.1501.

3,5-dimethyl-4-((5-methylthiophen-2-yl)methyl)-1-phenyl-1*H*-pyrazole (6g). Colourless liquid, yield = 35 % (57 mg). R_f 0.5 (EtOAc:*n*-Hexane = 0.5:9.5). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.39 (m, 1H), 7.34-7.30 (m, 1H), 6.53 (s, 2H), 3.86 (s, 1H), 2.40 (s, 3H), 2.25 (d, *J* = 6.1 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.9, 142.1, 140.1, 137.8, 136.6, 129.0, 127.1, 124.8, 124.6, 123.7, 116.6, 24.3, 15.3, 11.9, 11.0 ppm. HRMS (ESI) Calcd for $C_{17}H_{19}N_2S$ $[M+H]^+$ 283.1263; found 283.1272.

3,5-dimethyl-4-((3-methylthiophen-2-yl)methyl)-1-phenyl-1*H*-pyrazole and 3,5-dimethyl-4-((4-methylthiophen-2-yl)methyl)-1-phenyl-1*H*-pyrazole (6h). Colourless liquid, yield = 40 % (65 mg). R_f 0.5 (EtOAc:*n*-Hexane = 0.5:9.5). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 0.28 H), 7.44 (d, *J* = 6.1 Hz, 4H), 7.42 (s, 0.35 H), 7.34 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.01 (d, *J* = 5.1 Hz, 1H), 6.80 (d, *J* = 5.1 Hz, 1H), 6.68 (s, 0.21H), 6.56 (s, 0.23 H), 3.89 (s, 0.54 H), 3.83 (s, 2H), 2.26 (s, 0.73 H), 2.25 (s, 3 H), 2.23 (d, *J* = 3.5 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.9, 144.3, 140.1, 138.2, 137.4, 136.7, 132.2, 130.0, 129.0, 127.2, 126.5, 124.9, 121.6, 118.5, 116.6, 24.3, 22.4, 15.8, 13.8, 12.0, 11.0 ppm. HRMS (ESI) Calcd for $C_{17}H_{19}N_2S$ $[M+H]^+$ 283.1263; found 283.1274.

2-((3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)-1-methyl-1*H*-benzo[d]imidazole (6i). Colourless liquid, yield = 30 % (55 mg). R_f 0.5 (MeOH: DCM = 2:8). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.84–7.59 (m, 3H), 7.56–7.36 (m, 4H), 5.65 (s, 1H), 4.27 (s, 2H), 2.36 (d, *J* = 37.9 Hz, 6H), 2.17 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.8, 139.8, 139.1, 132.5, 131.1, 129.2, 128.1, 127.0, 125.2, 113.1, 112.7, 109.4, 42.4, 31.1, 12.4, 11.2 ppm. HRMS (ESI) Calcd for $C_{20}H_{21}N_4$ $[M+H]^+$ 317.1761; found 317.1777.

4-(benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole and 4-(benzo[b]thiophen-3-ylmethyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (6j). Yellow liquid, yield = 38 % (70 mg). R_f 0.5 (EtOAc:*n*-Hexane = 9.5:0.5). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 0.16 H), 7.65 (d, *J* = 7.9 Hz, 0.20 H), 7.46 (d, *J* = 4.1 Hz, 0.5 H), 7.40 (d, *J* = 4.5 Hz, 0.81 H), 7.36 (dd, *J* = 10.4, 5.9 Hz, 1.69 H), 7.29 (d, *J* = 8.0 Hz, 0.23 H), 7.26 (s, 1.58 H), 6.96 (s, 0.16 H), 6.84 (s, 0.95 H), 4.03 (s, 0.34 H), 3.95 (s, 2H), 2.28 (d, *J* = 4.0 Hz, 1.09 H), 2.23 (d, *J* = 7.4 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.3, 148.0, 145.6, 140.9, 140.1, 138.7, 136.9, 135.0, 129.0, 127.2, 127.2, 124.9, 124.8, 124.3, 124.1, 124.0, 123.6, 123.0, 122.9, 122.1, 121.5, 120.5, 114.8, 30.9, 25.1, 23.1, 12.0, 11.1 ppm. HRMS (ESI) Calcd for $C_{20}H_{19}N_2S$ $[M+H]^+$ 319.1263; found 319.1276.

General Procedure for Gram Scale Synthesis of Symmetric Bis-pyrazoles (Table 2, entry 2a). A dry round bottom flask (50 ml) was charged with 3,5-dimethyl-1-phenyl-1*H*-pyrazole (4.0 g, 23.26 mmol), oxone® (14.28 g, 23.26 mmol)) in DMSO (10 ml) at 150 °C in oil-bath for 2.5 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was purified using silica gel (ethyl acetate: *n*-hexane) to give the desired symmetric bis-pyrazole product (**2a**, 4.47 g, 54%).

The KIE Experiment. A dry round bottom flask (25 ml) was charged with pyrazole (100 mg, 0.581 mmol), oxone (356 mg, 0.581 mmol)) in DMSO (2 ml), DMSO-d_6 (2 ml) at 150 °C for 2 h. After completion (monitored by TLC), the reaction mixture was dried under vacuum, dissolved in ethyl acetate and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was analyzed by ^1H NMR for determination of K_H/K_D value (Scheme S9).

ASSOCIATED CONTENT

Supporting Information

DFT study, X-ray crystal structure data of 3j, characterization data of all compounds; ^1H and ^{13}C NMR and HRMS spectra. (PDF)

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