*Available online at* www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

**Der Pharma Chemica, 2017, 9(9):102-108**
*(http://www.derpharmachemica.com/archive.html)*

# Synthesis of 1-(Methylsulfonylmethyl)-4-aryl -1*H*-pyrazole Derivatives Using Ruphos-Pd as Catalyst

**Bijivemula N Reddy, Reddy SM, Madhvesh Pathak***

*School of Advanced Science, Vellore Institute of Technology, Vellore-632014, Tamil Nadu, India*

**ABSTRACT**

*A novel serious of 1-(methylsulfonylmethyl)-4-aryl -1H-pyrazole derivatives were synthesized efficiently by Suzuki coupling of the 4-bromo-1-((methylsulfonyl) methyl)-1H-pyrazol- with various aryl boronic acids in the presence of Ruphos-Pd as a catalyst. The reaction is usually furnished within 3 min with good to excellent isolated yields. All synthesized compounds were characterized by spectral techniques, like Proton Nuclear Magnetic Resonance ($^1$H NMR), $^{13}$C NMR and Liquid Chromatography–Mass Spectrometry (LC-MS) and also evaluate the antibacterial activity by disc diffusion method using two different bacteria's Pseudomonas aeruginosa (Gram-negative) and Staphylococcus aureus (Gram-positive). Most of the synthesized compounds shown good antibacterial activity against the standard penicillin drug.*

**Keywords:** (1-((Methylsulfonyl) methyl)-1H-pyrazol-4-yl) boronic acid, Suzuki coupling, Ruphos-P

## INTRODUCTON

Pyrazoles and substituted pyrazole derivatives have received much attention because they exhibit useful pharmacological properties and they are extensively using in the pharmaceutical industry and agrochemical since last few decades [1-3]. Therefore, several biologically important pyrazole-containing scaffolds are being developed as drugs for the treatment of various deceases, such as, antifungal, metabolic, central nervous system, oncological diseases, antimicrobial, antiprotozoal, cyclic-dependent kinase inhibitors, antimalarial, estrogen receptor modulators, anti-HIV, analgesic, anticancer, antihypertensive, antiparasitic, cardiotonic, antiviral, neurotropic, antihistaminergic, tuberculostatic, and anti-inflammatory. Since these huge biological activities, design and synthesis of pyrazole derivatives are an important area for a chemist. In this connection, there are several methodologies were reported for the synthesis of various pyrazole core units in literature. One of the best method/procedure is the coupling of various aromatic substitutions to the pyrazole core unit by direct pyrazole-aromatic linkages are reported in past few decades. For example, Negishi and Suzuki coupling are the best useful approaches for it with good product yields [4-17].

Recently, Microwave Assisted Organic Syntheses (MAOS) technique is one of the most important and fertile applications and has been broadly using in an organic synthesis which has advantages that are the reaction time from hours to minutes, reduce side reactions, increase yields and improve reproducibility [1,14-16]. In this connection, microwave-assisted Suzuki reaction can be considered as an efficient synthetic methodology for pyrazole-aromatic linkages today [17-21]. Recently, also reported the reaction between *N*-protected iodo pyrazolo with various aryl boronic acids under microwave source and got moderate yields [22].

It was, therefore, thought worthwhile to undertake the synthesis of some pyrazole derivatives possessing a methyl sulphonyl and pyrazolyl moieties to frame potential biological molecules and to use MAOS for them. Keeping in view of growing interest in the reactions of significance available in literature and numerous biological properties possessed by them, we became interested in developing an efficient method. Herein, we report a detailed account of results of our investigations on the multistep synthesis, *via* trans metal catalyzed cross-coupling of 4-bromo -((methylsulfonyl) methyl)-1*H*-pyrazole (4) with various aryl boronic acids (5a-n) catalyzed by the chloro(2-dicyclohexylphosphino-2′, 6′-diisopropoxy-1, 1′-biphenyl) [2-(2-amino-1,1′-biphenyl] palladium (II) (RuPhos-Pd G2). The reaction is usually finished in 5 min with good to excellent isolated product yields which are well characterized by spectral and analytical data and evaluated their antibaerial activity.

## MAERIALS AND MEHODS

All the chemicals, solvents, and reagents were procured from Sigma-Aldrich (Hyderabad, India), Merck (Mumbai, India), Lancaster Chemical (Mumbai, India) and SD fine chemicals and used as such without further purification. All used solvents for spectroscopic and other physical studies were reagent grade and were further purified by employing the reported methods. Melting points were recorded on Mel-Temp apparatus. All the Infrared spectra of the title compounds were recorded on Brucker Alpha-Eco (Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR) interferometer with single reflection sampling module equipped with KBr crystal.

All the NMR spectra were recorded on Bruker 400 MHz and 300 MHz spectrometer operating at 400 MHz and 300 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR. The compounds were dissolved in $CDCl_3$ and DMSO-$d_6$; the chemical shifts were referenced to TMS. Coupling constants were calculated in hertz (Hz) and finally the mass spectra were recorded on Agilent LC/MSD SL 1100 instrument.

*Synthesis of 4-bromo-1((mehylthio)mehyl)-1h-pyrazole (27)*

To a stirred solution of 4-bromo-1*H*-pyrazole (**1**, 10.0 g, 68.04 mmol) in 1,4-dioxane (100 ml) was added sodium carbonate (21.6 g, 204 mmol) at room temperature and stirred for 30 min. Then, a solution of (chloromethyl) (methyl) sulfane (**2**, 6.79 g, 70.4 mmol) in dioxane (30 ml) was added dropwise to the reaction mixture at 0°C. After completion of the addition resulted mixture was reflux for 3 h. Solvent was concentrated under reduced pressure to afford the residue. The obtained residue was diluted with water (100 ml) and extracted with ethyl acetate (2 × 100 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated the filtrate under reduced pressure to get a crude product. The crude product was purified by column chromatography to afford pure 4-bromo-1-((methylthio) methyl)-1*H*-pyrazole (**3**, 18.0 g, 84%) as off-white solid.

Off – White solid; 142-146°C (KBr); 3018, 1430, 1360 1350, 1118 and 940; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.62 (s, 1H, CH), 7.45 (s, 1H, CH), 5.05 (s, 2H, $CH_2$), 2.19 (s, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 140.7, 130.6, 93.9, 55.8 and 16.2. MS: (*m/z*=207, $[M+H]^+$).

*Synthesis of 4-bromo-1((mehylsulfonyl) mehyl)-1h-pyrazole (28)*

To a stirred solution of **6** (10 g, 48.3 mmol) in DCM (200 ml) was added *m*-CPBA (60%, 16.6 g, 96.6 mmol) pinch wise at 0°C and stirred at RT for 3 h. After that the reaction mixture was diluted with sat sodium bicarbonate solution (200 ml) and extracted with DCM (2 × 200 ml). The combined organic layer was washed with water twice (2 × 50 ml) and dried over anhydrous sodium sulfate and the solvent was concentrated under reduced pressure to afford crude product. The crude product was triturated with hexane (50 mL) to afford 4-bromo-1-((methylsulfonyl) methyl)-1*H*-pyrazole (28, 10 g, 86.5%) as off-white solid.

Off – White solid; mp: 157-160°C; IR (KBr); 3020, 1440, 1370. 1330. 1123 and 934; $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.59 (s, 1H), 5.73 (s, 2H), 3.01 (s, 3H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 142.7, 131.6, 96.0, 69.8, 39.2. MS: (*m/z*=238.7, $[M+H]^+$).

**Synthetic procedure for the model reaction**

*4-(2-(cyclopropylmehoxy) phenyl)-1-((mehylsulfonyl) mehyl)-1h-pyrazole (28a)*

*Method 1: MWI heaing method*

A dry Pyrex tube was charged with of 4-bromo-1-((methylsulfonyl) methyl)-1*H*-pyrazole (28, 100 mg, 0.42 mmol), (2-(cyclopropylmethoxy)phenyl)boronic acid (29a, 88 mg, 0.46 mmol), $K_3PO_4$ (178 mg, 0.84 mmol) and Silica Cat P-DPP (1 mol%) under argon and 1, 4-dioxane/water (2 ml/0.2 ml) were added and fitted with silicone rubber cap. The resulting mixture in the Pyrex tube was placed in a CEM Microwave reactor at 100 W powers (120°C) for 5 min. After complection of reaction, the catalyst was filtered, rinsed with DCM, dried under vacuum. The organic phase was separated and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated to get crude residue, and purified by silica gel chromatography using hexane-ethyl acetate. The obtained fractions are concentrated and dried in vacuum to get 144 mg (yield, 96%) of 4-(2-(cyclopropylmethoxy) phenyl)-1-((methylsulfonyl) methyl)-1*H*-pyrazole (30a).

*Method 2: Conventional method*

All the reactants are taken and the workup of the product (6a) was done as like MWI and heated to reflux in an oil bath at 40°C-110°C for 180-60 min.

Off-White solid; mp: 144-148°C; IR (KBr); 3149, 3062, 3020, 2917, 2310, 1612, 1106, 940 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 8.26 (s, 1H, CH, pyrazole), 8.09 (s, 1H, CH, pyrazole), 7.54 (d, J=7.8 Hz, 1H, Ar-H), 7.25-7.18 (m, 1H, Ar-H), 6.97 (t, J=7.5 Hz, 1H, Ar-H,), 6.90 (d, J=8.7 Hz, 1H, Ar-H), 5.31 (s, 2H, -$CH_2$), 3.90 (d, J=6.9 Hz, 2H, $OCH_2$), 2.88 (s, 3H, -$CH_3$), 1.38-1.33 (m, 1H,-CH,), 0.72-0.65 (m, 2H, $CH_2$), 0.40-0.35 (m, 2H, $CH_2$). $^{13}$C NMR (400 MHz, $CDCl_3$) δ: 155.4, 140.2, 130.7, 128.0, 127.3, 121.1, 120.8, 120.1, 112.3, 73.2, 70.1, 39.2, 10.4, 3.3; LCMS: 99.25% (*m/z*=306.95, $[M+H]^+$.

**General procedure for synthesis of (substituted-phenyl)-1-(methylsulfonylmethyl)-1h-pyrazole (28b-n)**

As like model reaction the 4-bromo-1-((methylsulfonyl) methyl)-1*H*-pyrazole (4, 100 mg, 0.42 mmol) and various aryl boronic acids (5b-s, 0.42 mmol) were mixed thoroughly with 1 mol% Silica cat PD-DPP and $K_3PO_4$ (2.0 equivalent) with isopropanol/$H_2O$ (2 ml/0.2 ml) in a Pyrex tube sealed with an air-tight silicone rubber cap and exposed to MWI at 100 W and 110°C under ambient pressure. TLC was shown the reaction completion in 5-7 min. The product separation and purification were done according to MWI method. The pure products were obtained from recrystallization by diethyl ether. All the structures of newly synthesized compounds were characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectral, and elemental analysis.

*4-(3, 5-difluorophenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30b)*

Off-White solid; mp: 124-128°C; IR (KBr); 3140, 3050, 3015, 2901, 1615, 1122, 937 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 7.86 (s, 1H, CH), 7.84 (s, 1H, CH), 7.0 (d, J=8.4 Hz, 2 H, Ar-H), 6.67 (t, J=8 Hz, 1H, Ar-H) 5.30 (s, 2H, $CH_2$), 2.92 (s, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 165.2, 165.0, 139.5, 134.4, 128.8, 123.6, 108.7, 108.6, 102.4,102.1, 69.8, 39.30; LCMS: 99.02% (*m/z*=272.96, $[M+H]^+$).

*4-(4-methoxyphenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30c)*

Off-White solid; mp: 154-158°C; IR (KBr); 3130, 3039, 2909, 1619, 1101, 944 $cm^{-1}$ ; $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.84 (s, 1H, CH), 7.83 (s, 1H, CH), 7.43 -7.40 (m, 2H, Ar-H), 6.94-6.91 (m, 2H, Ar-H), 5.29 (s, 2H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 2.89 (s, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ:157.3, 149.3, 139.49, 132.5, 132.2, 128.9, 126.2, 114.7, 113.9, 69.95, 55.9, 39.5. LCMS: 99.88 % (*m/z*=267.05, $[M+H]^+$).

*1-(methylsulfonyl methyl)-4-(naphthalen-1-y l)-1H-pyrazole (30d)*

Off- white solid; mp: 168-172; IR (KBr); 3135, 3034, 2914,1630, 1110, 940 $cm^{1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ: 8.03 (d, J=1.8 Hz, 2H, CH), 7.95 (s, 1H, CH), 7.83 (s, 1H, Ar-H), 7.83 (t, J=4.2 Hz, 2H, Ar-H), 7.61 (dd, $J_1$=1.5Hz, $J_2$=8.4 Hz, 1H, Ar-H), 7.50-7.43 (m, 2H, Ar-H), 5.34 (s, 2H, $CH_2$), 2.92 (s, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 139.8, 133.6, 132.5, 132.1, 132.0, 128.7, 128.5, 128.4, 127.6, 127.7, 126.5, 125.8, 125.4, 124.3, 124.0, 70.0, 39.2. LCMS: 95.77% (*m/z*=286.99, $[M+H]^+$).

*4-(5-fluoro-2-methylphenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30e)*

Off-White solid; mp: 116-120°C; IR (KBr, $cm^{-1}$); 3120, 3031, 2917, 1625, 1109, 937; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$=7.78 (s, 1H, CH), 7.76 (s, 1H, CH), 7.23-7.18 (m, 1H, Ar-H), 7.61 (dd, $J_1$=2.7Hz, $J_2$=9.6 Hz, 1H, Ar-H), 6.92 (t d, $J_1$=2.7 Hz, $J_2$=8.7 Hz, 1H, Ar-H), 5.32 (s, 2H, $CH_2$) 2.92 (s, 3H,$CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 162.3, 141.5, 132.5, 132.2, 130.9, 130.3, 123.6, 115.6, 114.0, 69.8, 39.3, 20.5. LCMS: 99.68% (*m/z*=268.98, $[M+H]^+$).

*4-(2-ethoxy-5-fluorophenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30f)*

Off white solid; mp: 161- 164°C ; IR (KBr, $cm^{-1}$); 3132, 3035, 2922, 1639, 1115, 943; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$=8.19 (s, 1H, CH), 8.01 (s, 1H, CH), 7.26-7.21 (m, 1H, Ar-H), 6.91-6.86 (m, 2H, Ar-H), 5.31 (s, 2H, $CH_2$), 4.13-4.06 (m, 2H, $OCH_2$), 2.89 (s, 3H, $CH_3$), 1.53-1.47 (m, 3H, $CH_3$). $^{13}$C NMR (400 MHz, $CDCl_3$) δ: 158.2, 155.8, 151.5, 140.8, 130.9, 121.4, 121.4, 120.2, 113.9, 113.7, 113.1, 113.1, 69.9, 64.4, 39.2, 14.9; LCMS: 92.25% (*m/z*=298.93, $[M+H]^+$).

*4-(3-ethoxy-5-fluorophenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30g)*

Off white solid; mp: 169- 173°C ; IR (KBr, $cm^{-1}$); 3130, 3035, 2924, 1635,1114,940; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$=7.84 (s, 1H, CH), 7.83 (s, 1H, CH), 7.11-6.97 (m, 3H, Ar-H), 5.29 (s, 2H, $CH_2$), 4.18-4.11 (m, 2H, $OCH_2$), 2.90 (s, 3H,$CH_3$), 1.54-1.45 (m, 3H); $^{13}$C NMR (400 MHz, $CDCl_3$) δ: 155.2, 150.8, 147.3, 147.2, 139.6, 128.1, 127.8, 127.7, 124.8, 118.4, 118.3, 116.7, 116.5, 112.6, 112.6, 69.9, 65.1, 39.2, 14.8; LCMS: 96.64% (*m/z*=298.97, $[M+H]^+$).

*4-(2, 3-dihydrobenzofuran-5-yl)-1-(methylsulfonylmethyl)-1H-pyrazole (30h)*

Off-White solid; mp: 135- 139°C ; IR (KBr, $cm^{-1}$); 3134, 3040, 2930, 1629, 1107 936; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$=7.81 (s, 1H, CH), 7.80 (s, 1H, CH), 7.33 (s, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 6.8 (d, J=8.1 Hz, 1H, Ar-H). 5.28 (s, 2H, $CH_2$), 4.60 (t, J=8.7 Hz, 2H, $OCH_2$), 3.23 (t, 8.7 Hz, 2H, Ar-$CH_2$), 2.88 (s, 3H,$CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 157.2, 130.2, 129.9, 128.0, 127.8, 127.6, 125.9, 125.2, 115.8, 70.0, 67.9, 39.3, 32.5 LCMS: 94.25% (*m/z*=279.09, $[M+H]^+$).

*4-(2-chlorophenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30i)*

Off-White solid; mp:118- 122°C; IR (KBr, $cm^{-1}$); 3137, 3030, 2939, 1635, 1112, 937; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$=8.07 (s, 1H, CH), 7.94 (s, 1H, CH), 7.47 (d, J=1.6 Hz, 1H, Ar-H), 7.45 (d, J=1.2 Hz, 1H, Ar-H), 7.31- 7.24 (m, 1H, Ar-H). 7.23 (d, J=2.0 Hz, 1H, Ar-H), 5.32 (s, 2H, $CH_2$), 2.92 (s, 3H, $CH_3$); 13C NMR (400 MHz, $CDCl_3$) δ: 141.7, 132.0, 130.9, 130.4, 130.0, 129.9, 128.4, 127.1, 122.0, 69.9, 39.3. LCMS: 79.28% (*m/z*=271.01, $[M+H]^+$).

*4-(furan-3-yl)-1-(methylsulfonylmethyl)-1H-pyrazole (30j)*

Brown solid; mp: 101-105°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$=7.75(s, 1H, CH), 7.73 (s, 1H, CH), 7.61 (s, 1H, Ar-H), 7.45 (d, J=1.5 Hz, 1H, Ar-H), 7.52 (d, J=1.2 Hz, 1H, Ar-H), 5.28 (s, 2H, $CH_2$), 2.88 (s, 3H,$CH_3$); $^{13}$C NMR (400 MHz, $CDCl_3$) δ: 143.6, 139.9, 138.2, 128.1, 116.5, 116.4, 109.2, 69.8, 39.1; LCMS: 79.28% (*m/z*=226.93 [M+H].

*4-(3, 4-dimethoxyphenyl)-1-(methylsulfonylmethyl)-1H-pyrazole (30k)*

Off-White solid; mp: 102-106°C; IR (KBr,$Cm^{-1}$); 3132, 3040, 2934, 1640, 1118 and 930; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$=7.84 (s, 2H, CH), 7.05 (d, d, $J_1$=2.0 Hz, $J_2$=6.0 Hz, 1H,Ar-H), 6.98 (d, J=2.4 Hz, 1H, Ar-H), 6.90 (d, J=7.6 Hz, 1H, Ar-H), 5.29 (s, 2H, $CH_2$), 3.94 (s, 3H,$OCH_3$), 3.90 (s, 3H,$OCH_3$), 2.90 (s, 3H,$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 149.3, 148.4, 139.5, 132.1, 128.4, 127.6, 118.3, 111.6, 109.3, 69.9, 55.9, 39.1, 39.3; MS: (*m/z*=297, $[M+H]^+$).

*2-(1-(methylsulfonylmethyl)-1H-pyrazol-4-yl) benzonitrile (30l)*

Light brown solid; mp. 109-113°C; IR (KBr, $cm^{-1}$): 3053, 2925, 2232, 1601, 1107 936; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$=7.95(s, 1H, CH), 7.91 (s, 1H, CH), 7.74 (m, 1H, Ar-H), 7.55 -7.50 (m, 1H, Ar-H), 7.32 (s, 1H, Ar-H). 5.31 (s, 2H, $CH_2$), 2.92 (s, 3H, $CH_3$); $^{13}$C NMR (400 MHz, $CDCl_3$) δ: 139.4, 132.6, 130.5, 129.9, 129.8, 129.1, 128.8, 123.3, 118.5, 113.2, 69.8 and 39.3. MS: (*m/z*=262, $[M+H]^+$).

*1-(methylsulfonylmethyl)-4-o-tolyl-1H-pyrazole (3m)*

Off- white solid: mp: 95-98°C; IR (ZnSe): ν 3053 (Ar-C-H), 2925 (ali C-H), 2232 (CN), 1601 (Ar-C=C), 1107 (C-O) $cm^{-1}$$^1$H NMR (300 MHz, $CDCl_3$) δ: 7.76 (s, 2 H), 7.33 (t, J=5.1 Hz, 1 H), 7.24-7.21 (m, 3H), 5.32 (s, 2H), 2.91 (s, 3H), 2.39 (s, 3H).$^{13}$C NMR (400 MHz, $CDCl_3$) δ: 141.72, 135.40, 130.78, 130.09, 129.14, 127,46, 127.46, 126.11, 124.40, 69.90, 39.23, 21.12. LCMS: 99.02 % (*m/z*=251.10, $[M+H]^+$). Anal. Calculated for $C_{12}H_{14}N_2O_2S$; C, 57.58; H, 5.64; N, 11.19; found: 57.50; H, 5.60; N, 11.15.

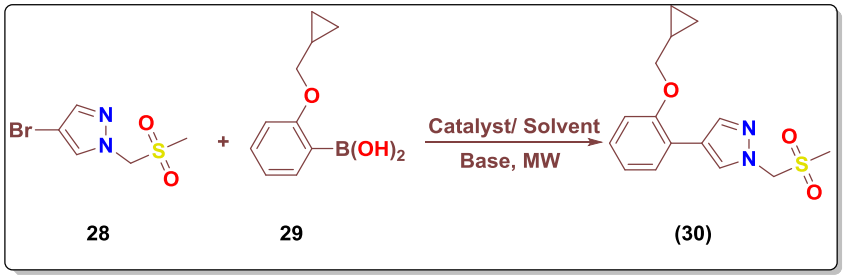
*1-(methylsulfonylmethyl)-4-phenyl-1H-pyrazole (3n)*

Off- white solid; Mp. 83-87°C; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 2H), 7.50 (d, J=7.2 Hz, 2H), 7.39 (t, J=7.8 Hz, 2H), 7.29 (d, J=7.5 Hz, 1H), 5.30 (s, 2H), 2.90 (s, 3H).; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 139.6, 131.2, 129.0, 128.1, 127.2, 125.8, 125.5, 70.0, 39.2; LCMS: 99.58% (*m/z*=236.97, $[M+H]^+$).

## RESULTS AND DISCUSSION

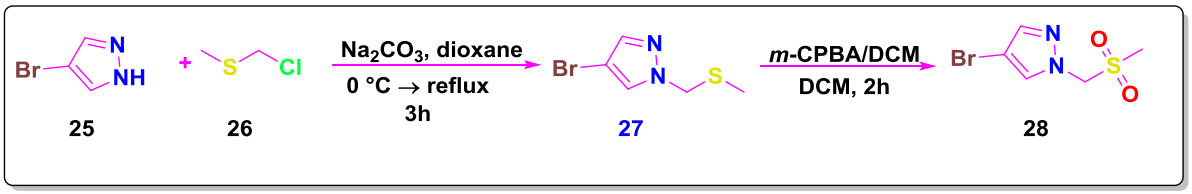
### Chemistry

At first, we designed and developed an efficient cross-coupling methodology for the synthesis of a new class of bioactive pyrazole derivatives (**30a-n**). Herein, we are chosen (4-bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazole (28 and boronic acid-2(cyclopropylmethoxy) benzene (2a) as substrates for the model reaction to obtain the cross-coupling product, 4-(2-(cyclopropylmethoxy) phenyl)-1-((methylsulfonyl) methyl)-1*H*-pyrazole (30a) and used various catalysts, solvents and base mediums under conventional (thermal) and microwave irradiation (MWI) conditions to develop the optimal reaction conditions for this methodology (Scheme 1).




**Scheme 1: Optimal reaction**

In the above model reaction one of the substrate, 4-bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazole (20), was previously prepared in two steps process from easily available materials (Scheme 2). At first, commercially available 4-bromo-1*H*-pyrazole (25) is treated with (chloromethyl)(methyl)sulfane (26) in the presence of $Na_2CO_3$ and obtained 4-bromo-1-(methylthiomethyl)-1*H*-pyrazole (27) in good yield (84.1%). Then the 3 was treated with *m*-CPBA to afford 4-bromo-1-((methylsulfonyl) methyl)-1*H*-pyrazole (28, 86.5%).




**Scheme 2: Synthesis of 4-bromo-1-((methylsulfonyl) methyl)-1H-pyrazole (28)**

**Table 1: Base and solvent effect on RuPhos-Pd G2 catalyzed Suzuki cross-coupling reaction[a,b]**

| Entry | Base | Solvent | Yield (%)[c] | |
|---|---|---|---|---|
| | | | Oil bath | MWI |
| 1 | $Na_2CO_3$ | Toluene/$H_2O$ | 62 | 82 |
| 2 | $Na_2CO_3$ | 1,4-dioxane/$H_2O$ | 65 | 83 |
| 3 | $Na_2CO_3$ | ACN/$H_2O$ | 69 | 83 |
| 4 | $Na_2CO_3$ | DME/$H_2O$ | 67 | 80 |
| 5 | $Na_2CO_3$ | EtOH/$H_2O$ | 66 | 80 |
| 6 | $Cs_2CO_3$ | Toluene/$H_2O$ | 70 | 88 |
| 7 | $Cs_2CO_3$ | 1,4-dioxane/$H_2O$ | 70 | 89 |
| 8 | $Cs_2CO_3$ | ACN/$H_2O$ | 68 | 86 |
| 9 | $Cs_2CO_3$ | DME/$H_2O$ | 64 | 82 |
| 10 | $Cs_2CO_3$ | EtOH/$H_2O$ | 65 | 82 |
| 11 | $K_3PO_4$ | Toluene/$H_2O$ | 71 | 94 |
| 12 | $K_3PO_4$ | 1,4-dioxane/$H_2O$ | 74 | 96 |
| 13 | $K_3PO_4$ | ACN/$H_2O$ | 72 | 93 |
| 14 | $K_3PO_4$ | DME/$H_2O$ | 73 | 94 |
| 15 | $K_3PO_4$ | EtOH/$H_2O$ | 72 | 94 |

[a]Reaction condition: boronic acids 2-(cyclopropylmethoxy) benzene (1.0 equiv.), (4-bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazole (1.0 equivalent), RuPhos-Pd G2 (1 mol%), base (3.0 equiv.) and solvent/$H_2O$ (3 ml/1 ml); [b]all the reactants are irradiated for 3 min with 100 W (120°C) microwaves and the thermal heating for 60 min by oil bath; [c]Isolated yields with >95% purity as determined by $^1$H NMR and LC–MS analysis

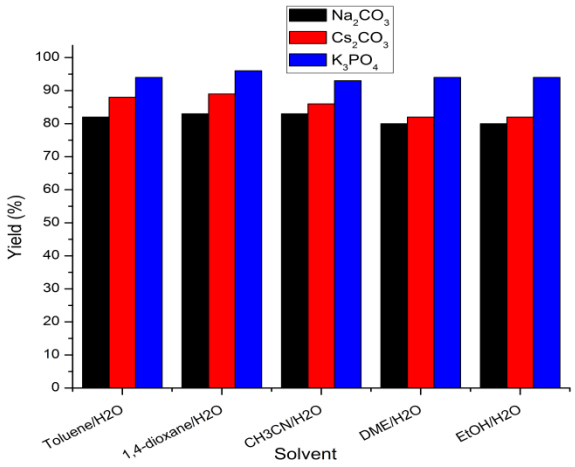



**Figure 1: Effect of solvent on catalytic activity of RuPhos-Pd G2 in Suzuki cross-coupling reaction**

After that, due to dramatic effects of RuPhos-Pd G2 (Figure 1) catalyst on yields of the model cross-coupling reaction in the presence of $K_3PO_4$ base (Table 1, entries 11-15) our efforts are focused again on screening of various palladium source catalysts in 1 mol% on the model reaction using 3 equivalent of $K_3PO_4$ under 100 W (120°C) MWI. Herein, we have tuned the effect of Pd catalysts on the model reaction (Table 2, entry 1-6) and find the RuPhos-Pd G2 is the best palladium source for this model reaction at 5 min (Table 3, entry 6). On the other hand, the other Pd catalysts which are utilized in this cross-coupling reaction showed lower yields even at higher reaction times (Table 3, entries 1-5). After that, we have further examined the RuPhos-Pd G2 catalyst on the model reaction at various amounts of catalyst and reaction times. But they are not resulted in better yields in either conditions either at higher or lower amount of catalyst or reaction times (Table 3, entries 7-11).

**Table 2: Optimization of Pd-catalyzed Suzuki coupling reaction conditions[a,b]**

| Entry | Pd source catalyst (mol%) | Time (min) | Yield[c] (%) |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ (1) | 7 | 30 |
| 2 | $Pd_2(dba)_3$ (1) | 8 | 32 |
| 3 | $Pd(PPh_3)_4$ (1) | 7 | 56 |
| 4 | $Pd(dppf)Cl_2$ (1) | 6 | 67 |
| 5 | $PdCl_2(PPh_3)_2$ (1) | 6 | 69 |
| 6 | RuPhos-Pd G2 (1) | 5 | 96 |
| 7 | RuPhos-Pd G2 (1) | 7 | 96 |
| 8 | RuPhos-Pd G2 (1) | 10 | 97 |
| 9 | RuPhos-Pd G2 (2) | 5 | 96 |
| 10 | RuPhos-Pd G2 (3) | 5 | 97 |
| 11 | RuPhos-Pd G2 (0.5) | 5 | 81 |

[a]Reaction conditions: 4-bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazol-4-yl) (4a, 1.0 equiv.) and boronic acid -2-(cyclopropylmethoxy) benzene (5a, 1.1 equiv.), and $K_3PO_4$ (3 equiv.); [b]all the reactants irradiated with 100 W (120°C) MWs for 3 min; [c]Isolated yields with > 95% purity as determined by $^1$H NMR and LC-MS

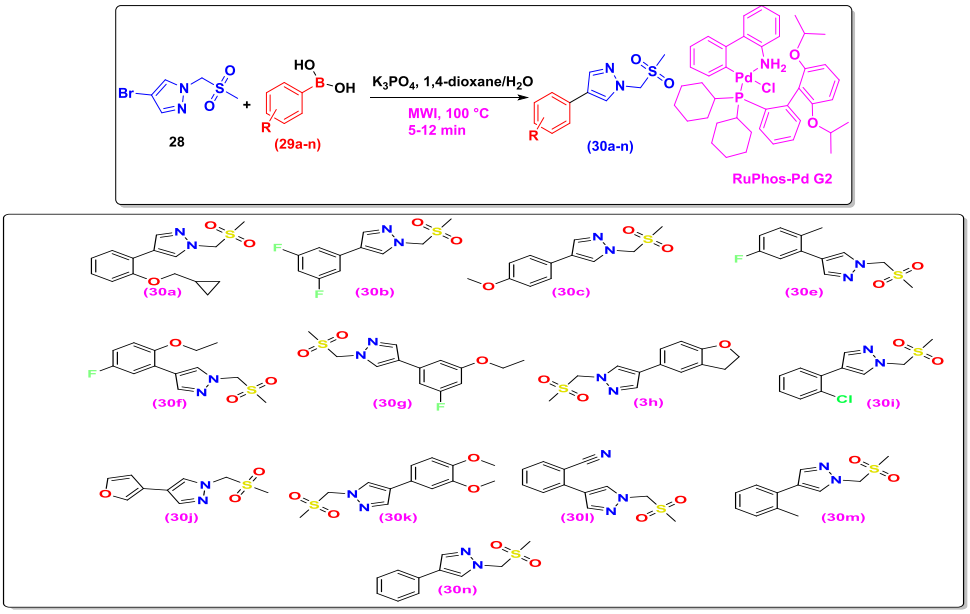
Next, we performed the effect of microwave irradiation on model reaction with comparing the conventional reaction conditions.

**Table 3: Effects of MW irradiation and conventional heating on model reactions[a]**

| Entry | Microwave irradiation | | | | Conventional (oil bath) heating | | |
|---|---|---|---|---|---|---|---|
| | MW power (W) | Temp. (°C) | Time (min) | Yield[b] (%) | Temp. (°C) | Time (min) | Yield[b] (%) |
| 1 | 80 | 100 | 15 | 75 | RT | 300 | 23 |
| 2 | 100 | 120 | 5 | 96 | 50 | 180 | 51 |
| 3 | 100 | 120 | 4 | 94 | 60 | 120 | 67 |
| 4 | 120 | 150 | 5 | 96 | 80 | 90 | 68 |
| 5 | 150 | 200 | 5 | 97 | 100 | 60 | 71 |
| 6 | 200 | 300 | 3 | 95 | 120 | 50 | 74 |
| 7 | 250 | 400 | 3 | 94 | 140 | 30 | 81 |

[a]Reaction conditions: boronicacid -2-(cyclopropylmethoxy) benzene (1.0 equiv.), (4- bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazol-4-yl) (1.0 equiv.), RuPhos-Pd G2 (1 mol%), $K_3PO_4$ (3.0 equiv.) and 1,4-dioxane/$H_2O$ (3 ml/1 ml); [b]Isolated yields with > 95% purity as determined by $^1$H NMR and LC–MS analysis

With the above optimized reaction conditions of the model reaction, we performed a series of cross-coupling reactions with4-bromo 1-((methylsulfonyl) methyl)-1*H*-pyrazol- (28) and various aryl boronic acids (29 b-n) using RuPhos-Pd G2 (1 mol%) catalyst and $K_3PO_4$ (3 equiv.) as base in 1,4-dioxane/$H_2O$ solvent medium under MW irradiation (100 W) for 5 min to obtained require compounds (Scheme 3). In most cases, the corresponding, 4-aryl-pyrazole derivatives are obtained in good to excellent yields.




**Scheme 3: Synthesis of (substituted-phenyl)-1-(methylsulfonylmethyl)-1*H*-pyrazole derivatives (30a–n)**

**Pharmacology**

**Antibacterial activity of synthesized (substituted-phenyl)-1-(mehylsulfonyl)-1h-pyrazole derivatives (30a-m)**

*In vitro* antibacterial activity of synthesized compounds (3a-m) were evaluated using the agar disc diffusion method [23-28] against selected pathogens, such as, *Pseudomonas aeruginosa* (Gram-negative), *Staphylococcus aureus* (Gram-positive) and the results are presented in Table 4. The titled compounds were dissolving in Dimethyl Sulfoxide (DMSO) and sterilized by filtering through 0.45 millipore filter. Nutrient agar was prepared and sterilized by an autoclave (121°C and 15 lbs for 20 min) and transferred to previously sterilized petri discs (9 cm diameter). After solidification petri disc plates were inoculated with bacterial organism in sterile nutrient agar medium at 45°C. The sterile Whatman filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized titled derivatives at a concentration of 250 and 500 mg/ml are placed in an organism impregnated Petri plates under sterile condition and the plates was left for 30 min to allow the diffusion of the derivatives at room temperature. The antibiotic disc of penicillin 100 mg/ml was used as a reference drug. Then the plates were incubated for 24 h at 37°C and the zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around each disc. Each test was carried out triplicate and noted average [23-28].

The results showed that most of the tested compounds were shown good antibacterial activity compared with standard drug, penicillin. By analysing tested results the antibacterial activity of the titled compounds mostly exhibiting the basic core unit of 1-((methylsulfonyl) methyl)-4-phenyl-1*H*-pyrazole. And on the other hand the substituents present at phenyl ring of core unit are also showing considerable effect.

**Table 4: Antibacterial activity of synthesized titled derivatives (30a-m)**

| S. No. | Sample | Zone of inhibition (mm) | | | |
|---|---|---|---|---|---|
| | | *Pseudomonas aeruginosa* | | *Staphylococcus aureus* | |
| | | 250 (mg/disc) | 500 (mg/disc) | 250 (mg/disc) | 500 (mg/disc) |
| 1 | 30a | 13.79 | 16.75 | 14.28 | 18.19 |
| 2 | 30b | 15.35 | 17.48 | 14.24 | 18.1 |
| 3 | 30c | 13.76 | 17.26 | 12.95 | 17.16 |
| 4 | 30d | 13.85 | 18.26 | 13.95 | 17.21 |
| 5 | 30e | 14.65 | 18.87 | 15.89 | 18.71 |
| 6 | 30f | 14.44 | 17.75 | 14.81 | 18.46 |
| 7 | 30g | 12.45 | 16.75 | 11.3 | 16.85 |
| 8 | 30h | 12.92 | 17.33 | 12.22 | 15.87 |
| 9 | 30i | 12.32 | 18.28 | 12.96 | 17.48 |
| 10 | 30j | 16.25 | 19.75 | 17.15 | 20.21 |
| 11 | 30k | 14.73 | 18.19 | 14.05 | 19.09 |
| 12 | 30l | 13.75 | 17.16 | 13.12 | 18.94 |
| 13 | 30m | 12.18 | 16.54 | 11.45 | 16.99 |
| 14 | Penicillin[a] | 21.23 | - | 22.86 | - |

[a]Reference compound. The synthesized compounds zone of inhibition observed in cup plates

## CONCLUSION

In summary, a series of novel 1-(methylsulfonylmethyl)-4-aryl -1*H* pyrazoles were synthesized by one step Suzuki cross-coupling reaction under microwave irradiation conditions using Ruphos-Pd G2 as an efficient catalyst. The procedure exhibits several advantages, such as mild reaction conditions, shorter reaction times, high efficiency of the catalyst, wide range of reactant tolerance and excellent product yields. Their structures were characterized $^{1}$H NMR, $^{13}$C NMR and LC-MS However, amongst the newly synthesized title compounds (6a-n) most of them was shown promising antibacterial activity against the standard penicillin drug.

## REFERENCES

[1] T.J. Hu, S. Chen, H.Y. Sun, J. Yang, Y. Rao, *Org. Lett*., **2012**, 14, 5030.
[2] J. Huang, T.J. Hong, R. Martin, S.L. Buchwald, *Acc. Chem. Res.*, **2008**, 41, 1461.
[3] H.S. Hong, *Eur. J. Org. Chem.*, 2012, 33, 6630.
[4] V.K. Aggarwal, J. de Vicente, R.V. Bonnert, *J. Org. Chem*., **2003**, 68, 5381-5383.
[5] S. Fustero, S.M. Rosell, P. Barrio, A.S. Fuentes, *Chem. Rev.*, **2011**, 111, 6984.
[6] M.C. Stellrecht, S.L. Chen, *Cancers.*, **2011**, 3, 4170.
[7] C.C. Selvam, M.S. Jachak, R. Thilagavathi, K.S. Chakraborti, *Bioorg. Med. Chem. Lett*., **2005**, 15, 1793.
[8] S.G. Kuo, L.J. Huang, H.J. Nakamura, *J. Med. Chem*., **1984**, 27, 539.
[9] M.A. Abdel-Aziz, O.H. Hishmat, Sh. I. El-Naem, N.M. fawzy, *Sulfur Lett*., **1990**, 10, 255.
[10] O.H. Hishmat, N.M. Fawzy, D.S. Farrg, A.S. Abd El All, A.H. Abdel-Rahman, *Boll. Chim. Farma*., **1999**, 138, 427-431.
[11] T. Zhang, X.S. Gao, H.B. Wood, *Tetrahedron Lett.*, **2011**, 52, 311.

[12] G.M. Organ, S. Mayer, *Comb. J. Chem*., **2003**, 5, 118.
[13] X. Wang, J. Tan, K. Grozinger, *Tetrahedron Lett*., **2000**, 41, 4713.
[14] C. Dvorak, D.A. Rudolph, *J. Org. Chem.*, **2005**, 70, 4188.
[15] D.K. James, S.J. Edeson, S. Stokes, *Org. Lett.*, **2012**, 14, 5354.
[16] M. Carlos, M. Javier, C. Mercedes, J.M. Mınguez, *Org. Lett*., **2010**, 12, 4924.
[17] T. Tang, A.G. Capacci, X.D. Wei, *Angew Chem Int Ed*., **2010**, 49, 5879.
[18] K. Bougrin, A. Loupy, *J. Photochem. Photobiol. C, Photochem. Rev.*, **2005**, 6, 139-167.
[19] D. Adam, *Nature*., **2003**, 421, 571.
[20] V. Marx, *Chem Eng News.*, **2004**, 82, 14-19.
[21] C.O. Kappe, *Angew. Chem. Int. Ed*., **2004**, 43, 6250.
[22] K.M. Dawood, *Tetrahedron*., **2007**, 63, 9642-9651.
[23] H.H. Nguyen, M. Kurth, *J. Org. Lett.*, **2013**, 15, 362.
[24] W. Chang, G. Chae, S.R. Jang, H. Shin, B.J.A. Ahn, *J. Ind. Eng. Chem*., **2012**, 18, 581.
[25] R.K. Arvela, N.E. Leadbeater, *Org Lett*., **2005**, 7, 2101.
[26] V.P. Mehta, E.V. van der Eycken, *Chem. Soc. Rev.*, **2011**, 40, 4925.
[27] M.C. Bagley, *Pharmaceuticals.*, **2015**, 8, 257-276.
[28] H. Cheng, W. Qiong-You, F. Han, Y. Guang-Fu, *Chin. Chem. Lett*., **2014**, 25, 705-709.