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MICROWAVE-INDUCED SUZUKI-COUPLING TOWARD PYRAZOLES

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Abstract: Pyrazoles have biological applications as anticancer, antimicrobial, antiviral, antifungal, anti-inflammatory, analgesic, and insecticidal agents. Microwave-assisted synthesis of numerous new pyrazoles is achieved following Suzuki-coupling reaction. The yield of this convergent method is high.

Key words: Microwave, Suzuki Coupling, Pyrazole

Introduction:

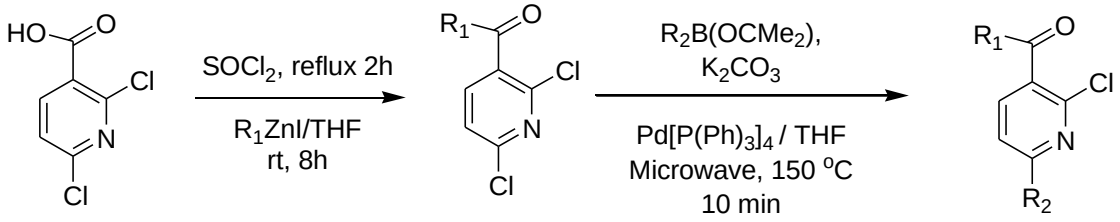
Over the past few decades, microwave-induced reactions have become an integral part of chemical research. These processes have been related to sustainable and green organic chemistry.[1-9] Microwave-assisted synthesis has numerous general benefits. These include significant rate enhancement; reduction of overall process time; increased yield of the products; improved product purity; minimized by-products formation; and high reproducibility rate.

Pyrazoles have a broad spectrum of pharmaceutical and biological applications such as anti-cancer, anti-inflammatory, anti-fungal, antibacterial, anti-insecticidal, analgesic, antiviral, anticonvulsant, anti-diabetic, antipyretic, anti-arrhythmic, anti-depressant, anti-hyperglycemic, anti-oxidant, and herbicidal agents.[10-18] There are several drugs in the market that contain pyrazole moiety. These include such Celecoxib,[19] Lonazolac,[20] Mepirizole,[21] Rimonabant,[22] acomplia,[23]Cimetidine,[24] Fipronil, [25] and Dexacoxib.[26] This paper reports microwave-assisted synthesis of pyrazoles through a single step reaction of hydrazine with benzylic ketones that have an chlorine connected to an aromatic ring. [27-40]

Results:

Structural diversity was first introduced by the condensation of 2,6-dichloro nicotinic acid chloride with various zinc halides (e.g., bromide or iodide) in the presence of tetrakis(triphenylphosphine)palladium in THF following Suzuki reaction (1 to 2).[41-46]A condensation between an aromatic chlorine with various boronate esters by means of a Suzuki coupling using microwave conditions at 150^{o}C for 5 min by the help of CEM microwave reactor was performed (2 to 3, Scheme 1). Under classical reaction conditions, this method was extremely sluggish.

Scheme 1: Synthesis of 2-arylpyridines via microwave-assisted Suzuki coupling reaction

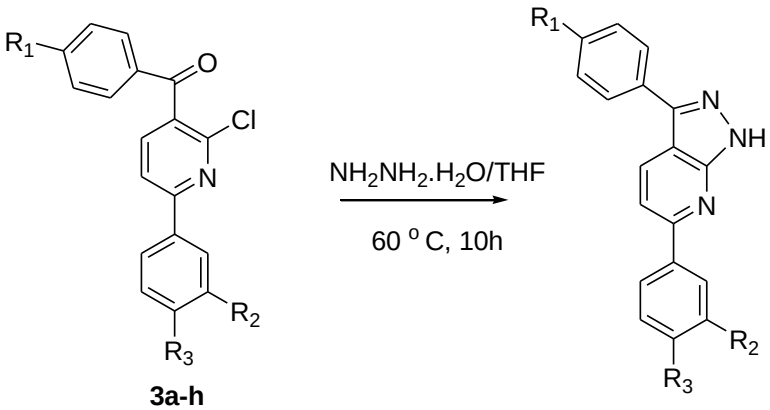


1 **2a-d** **3a-h**

R1 = 4-CO_2Et-C_6H_4, 4-OEt-C_6H_4, 4-OMe-C_6H_4, 4Br-C_6H_4
R2 = 3-NHAC-C_6H_4, 4-CO_2Et-C_6H_4,

A reaction of hydrazine with benzylic ketones 3a-h that have an chlorine connected to an aromatic ring produced the pyrazole 4 in excellent yield (Scheme 2).

Scheme 2: Synthesis of pyrazoles



3a-h **4**

R_1 = 4-CO_2Et, 4-OEt, 4-OMe, 4Br
R_2 = 3-NHAC, R_3 =H,
R_2 =H, R_3 = 4-CO_2Et

Experimental:

General Apparatus: Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded at ambient temperature on an IBM-Brucker Model NR/200 AF spectrometer in the Fourer transform model, in $CDCl_3$ using Me_4Si as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are in hertz (Hz). Melting points were determined on a Hoover capillary apparatus and are uncorrected. All reactions were carried out in dry glass were protected from atmospheric moisture. Solvents were dried over freshly activated (300^{o}C/1h) molecular sieves (type 4 A). The homogeneity of the products were determined by ascending TLC on silica-coated aluminium-backed plates (silica gel 60 F 254; Merck). Organic extracts of aqueous solutions were dried over anhydous Na_2SO_4. Solutions were concentrated under reduced pressure on a rotary evaporator.

Procedure for the synthesis of compounds by microwave irradiation:

Compound (**3a**): A mixture of (2,6-dichloro-3-pyridinyl)(4-ethyloxycarbonyll)methanone (300 mg, 0.93 mmol), 3'-(4,4,5,5-tetramethyl-1,3-2-dioxaborolan-2-yl)acetanilide, potassium carbonate (200 mg), tetrakis(triphenylphosphine)palladium (80 mg) in THF (4 mL) was finished with argon and then subjected to microwave at 155^{o}C for 10 min. The whole product was adsorbed onto silica, then purified by flash column chromatography over silica gel, using polarity gradient 5-50% EtOAc in hexane to yield acetanilide derivative (200 mg, 49%) as a yellow oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.32 (s, 1H), 7.81(m, 4H), 7.47 (t, 1H, J = 7.8 Hz), 7.10 (d, 2H, J = 9.0 Hz), 4.36 (q, 2H, J =7.2 Hz), 2.08 (s, 3H), 1.36 (t, 3H, J

= 7.2 Hz) ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5,60.8, 55.7, 14.2; MS ($C_{23}H_{19}ClN_2O_4$) calcd. 422.103 found MH^+ 423.2.
Compound (**3b**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.30 (s, 1H), 7.80 (m, 4H), 7.47 (t, 1H, J = 7.8 Hz), 7.10 (d, 2H, J = 9.0 Hz), 4.36 (q, 2H, J =7.2 Hz), 2.08 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz) ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 129.5, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 114.5, 60.8, 22.8, 14.2; MS ($C_{22}H_{19}ClN_2O_3$) calcd. 394.1084 found MH^+ 395.3.
Compound (**3c**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.32 (s, 1H), 7.81 (m, 4H), 7.47 (t, 1H, J = 7.8 Hz), 7.10 (d, 2H, J = 9.0 Hz), 3.87 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 55.7, 24.0; MS ($C_{21}H_{17}ClN_2O_3$) calcd. 380.0928 found MH^+ 381.2.
Compound (**3d**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.30 (s, 1H), 7.79 (m, 4H), 7.45 (t, 1H, J = 7.8 Hz), 7.09 (d, 2H, J = 9.0 Hz), 2.08 (s, 3H); ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 131.9, 131.8, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 22.9; MS ($C_{20}H_{14}BrClN_2O_2$) calcd. 427.9927 found MH^+ 429.1.
Compound (**3e**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.78 (m, 4H), 7.45 (t, 1H, J = 7.8 Hz), 7.09 (d, 2H, J = 9.0 Hz), 4.36 (q, 4H, J =7.2 Hz), 2.08 (s, 3H), 1.36 (t, 6H, J = 7.2 Hz); ^{13}C NMR δ 191.3, 168.5, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 133.0, 132.4, 132.3, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 60.8, 60.8, 14.2, 14.2; MS ($C_{24}H_{20}ClNO_5$) calcd. 437.1030 found MH^+ 438.2.
Compound (**3f**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.80 (m, 6H), 7.47 (t, 1H, J = 7.8 Hz), 7.10 (d, 2H, J = 9.0 Hz), 4.36 (q, 2H, J =7.2 Hz), 4.30 (q, 2H, J =7.2 Hz), 2.08 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 1.36 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 129.5, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 114.5, 60.8, 60.5, 14.7, 14.2; MS ($C_{23}H_{20}ClNO_4$) calcd. 409.1081 found MH^+ 410.2.
Compound (**3g**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.82 (m, 6H), 7.47 (t, 1H, J = 7.8 Hz), 7.10 (d, 2H, J = 9.0 Hz), 4.36 (q, 2H, J =7.2 Hz), 3.87 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 191.1, 168.3, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 129.5, 129.5, 128.4, 121.5, 120.8, 119.2, 117.3, 114.5, 114.5, 60.8, 55.6, 14.2; MS ($C_{22}H_{18}ClNO_4$) calcd. 395.0924 found MH^+ 396.2.
Compound (**3h**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.79 (m, 6H), 7.45 (t, 1H, J = 7.8 Hz), 7.09 (d, 2H, J = 9.0 Hz), 4.36 (q, 2H, J =7.2 Hz), 1.36 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 191.3, 168.5, 164.2, 157.4, 145.9, 140.1, 139.5, 136.8, 133.1, 132.3, 131.9, 131.8, 129.5, 128.4, 121.5, 120.8, 119.1, 117.1, 114.4, 60.6, 14.1; MS ($C_{21}H_{15}BrClNO_3$) calcd. 442.9924 found MH^+ 444.1.

Conclusion:

Microwave-induced synthesis is applied successfully for the preparation of various pyrazole in excellent yield. The preparation of these agents by classical method is a complicated process. In contrast, microwave-assisted method can be performed with numerous 2-chloropyrdine systems successfully and thus, several pyrazoles become readily available.

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