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Structural Identification of Pyrazoles and Pyrimidines Using 2D HMBC NMR and Single-Crystal X-Ray Diffraction

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A facile and highly efficient microwave-assisted synthesis of functionalized pyrazoles and pyrimidines based on the regiospecific synthesis is reported. The present work provides unambiguous evidence of the pyrazoles was determined using 2D HMBC NMR. The structure for pyrimidine have been confirmed by single-crystal X-ray diffraction.

Keywords: Microwave irradiation, Isoniazid, Pyrazoles, Pyrimidines.

INTRODUCTION

Among the many heterocyclic compounds that have been explored as potential pharmacologically active compounds, pyrazoles are known to have chemotherapeutic effects and function as antimicrobial[1], antifungal[2] and antiviral agents[3]. Pyrazoles are an important class of five-membered heterocyclic compounds and are widely found as the core structure in many agrochemicals and pharmaceuticals. Recently, pyrazole synthesis has been of interest because of their prevalence as scaffolds in the syntheses of bioactive compounds. Pyrazole derivatives have diverse biological activities[4-7] and are known as anticarcinogens[8]. Pyrimidines are also hetrocycles of interest because of their antimicrobial[9], antioxidant[10], antiinflammatory[11], antiallergic[12] and anticancer[10,13] activities.

The aim of the present study was to develop a facile and highly efficient microwave-assisted synthesis of functionalized pyrazoles and pyrimidines. The structures of the pyrazoles were determined using two-dimensional heteronuclear multiple-bond correlation nuclear magnetic resonance spectroscopy (2D HMBC NMR), and those of the pyrimidines were determined by X-ray crystallography.

EXPERIMENTAL

The IR spectra were run on a Smart iTR 100. NMR spectra were performed on Bruker 400 MHz. Mass spectra were recorded on Thermo Scientific Quantum Access. The elemental compositions were determined on a on a Euro Vector instrument. Microwave experiments were performed using CEM Discover (300 W). Single crystal X-ray analyses were performed using Bruker APEX2 instrument.

Chalcones **3a-d** were prepared according to the literature[13].

Synthesis of pyrazoles (5a-d): A mixture of chalcones **3a-d** (1 mmol), isoniazid (**4**) (1mmol) and AcOH (5 mL) was subjected to microwave heating for several minutes to afford pyrazoles.

(3-(4-Chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazolyl)(pyridin-4- yl)methanone (5a): m.p. 205-206 °C; IR (KBr, ν_{max}, cm^{-1}): 1642 (C=O), 1553 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ: 3.10 (dd, $1H_A$), 3.66 (dd, $1H_B$), 5.70 (dd, $1H_X$) , 7.01-8.69 (m, 11H, ArH); ^{13}C NMR δ: 41.33, 59.80, 123.21, 126.05 ,126.33, 126.90, 127.78, 128.11, 128.34, 128.70, 128.90, 132.91, 138.30, 142.46, 148.34, 148.50, 152.71, 164.33; MS: (%) 368 (M + 2, 75), 369 (M^+, 80). Calcd. for $C_{19}H_{14}N_3OSCl$: C, 62.11; H, 2.82; N, 10.42; Found: C, 61.77; H, 2.71; N, 9.87.

[3-(4-Hydroxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazolyl](pyridin-4-yl)methanone (5b): m. p. 168-170 °C; IR (KBr, ν_{max}, cm^{-1}): 1660 (C=O), 1560 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ: 3.12 (dd, H_A), 3.55 (dd, $1H_B$), 5.68 (dd, $1H_X$), 7.01-8.69 (m.11H, ArH); ^{13}C NMR δ: 42.31, 60.01, 122.96, 125.89, 126.30, 126.93, 127.81, 128.18, 128.44, 128.71, 128.93, 133.05, 137.50, 143.40, 147.80, 149.50, 153.88, 165.31; MS: (%) 349 (M^+, 85). Calcd. for $C_{19}H_{15}N_3O_2S$: C, 67.31; H, 3.33; N, 11.03; Found: C, 66.08; H,2.89; N, 10.88.

Pyridin-4-yl[5-(thiophen-2-yl)-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazolyl]methanone (5c): m.p. 172-173 °C, IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O), 1573 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ: 2.30 (s, 3H, Me), 3.29 (dd, H_A), 3.91(dd, H_B), 5.21 (dd, H_X), 7.01-8.69 (m.11H, ArH); ^{13}C NMR δ: 44.30, 61.11,

122.90, 125.77, 126.33, 126.90, 127.83, 128.92, 128.50, 128.78, 128.90, 133.15, 138.44, 142.54, 146.19, 149.88, 154.88, 166.33; MS: (%) 347 (M^+, 90). Calcd. for $C_{20}H_{17}N_3OS$: C, 69.13; H,4.94; N, 11.19; Found: C, 68.02; H, 4.85; N, 10.72.

[3-Phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-yl](pyridin-4-yl)methanone (5d): m.p. 183-185 °C; IR (KBr, ν_{max}, cm^{-1}): 1669 (C=O), 1560 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.36 (dd, H_A), 3.90 (dd, H_B), 5.11 (1H, H_X) , 7.01-8.69 (m.12H, ArH); ^{13}C NMR δ: 41.53, 60.20, 121.91, 124.79, 125.93, 126.91, 127.81, 128.92, 128.51, 128.78, 128.94, 132.16, 133.85, 139.43, 143.55, 146.43, 150.03, 154.59, 166.32; MS: (%) 333 (M^+, 80). Calcd. for $C_{19}H_{15}N_3OS$: C, 68.55; H, 2.53; N, 16.60; Found: C, 66.80; H, 2.18; N, 15.11.

Synthesis of pyrimidines (8a-d): A mixture of chalcones **3a-d** (1 mmol), guanidine hydrochloride (**7**) (1 mmol) and potassium hydroxide (4 mmol) in methanol (3 mL) was subjected to microwave heating for several minutes to afford pyrimidines.

4-(4-Chlorophenyl)-6-(thiophen-2-yl)pyrimidin-2-amine (8a): m.p. 164-165 °C; IR (KBr, ν_{max}, cm^{-1}): 3433 (NH_2), 1451 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.03 (s, 2H, NH_2), 7.93 (s, 1H, $H_{pyrimidin}$), 7.15-8.11 (m, 7HAr); ^{13}C NMR δ: 94.17, 127.33, 127.65, 128.21, 128.83, 130.51, 132.52, 135.52, 137.19, 142.60, 159.54, 163.14, 164.50; MS (%): 289 (M+2, 28), 287 (M^+, 80). Calcd. for $C_{14}H_{10}N_3SCl$: C, 59.44; H, 2.50; N, 15.55; Found: C, 58.43; H, 2.10; N,14.87.

4-(4-Hydroxyphenyl)-6-(thiophen-2-yl)pyrimidin-2-amine (8b): m.p. 139-140 °C; IR (KBr, ν_{max}, cm^{-1}): 3465 (NH_2), 1455 (C=N), ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.11 (s, 2H, NH_2), 7.89 (s, 1H, $H_{pyrimidin}$), 7.10-7.99 (m, 7HAr); ^{13}C NMR δ: 93.54, 127.30, 127.55, 128.71, 128.82, 130.51, 132.42, 134.92, 136.29, 142.50, 158.94, 162.94, 164.53; MS: (%) 269 (M^+, 95). Calcd. for $C_{14}H_{11}N_3OS$: C, 62.98; H,3.11; N, 14.50; Found: C, 62.18; H, 3.02; N, 13.17.

4-(Thiophen-2-yl)-6-*p*-tolylpyrimidin-2-amine (8c): m.p. 166-168 °C; IR (KBr, ν_{max}, cm^{-1}): 3454 (NH_2), 1465 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.33 (s, 3H, Me), 7.01 (s, $2H_{Amine}$), 7.88 (s, 1H, $H_{pyrimidin}$), 7.31-8.09 (m, 7HAr); ^{13}C NMR δ: 93.50, 127.41, 127.57, 128.66, 128.92, 130.71, 132.92, 135.92, 136.31, 142.60, 159.84, 162.84, 165.02; MS (%): 267 (M^+, 85). Calcd. % $C_{15}H_{13}N_3S$: C, 68.67; H, 4.16; N, 14.72; Found: C, 67.75; H, 4.11; N, 13.95.

4-Phenyl-6-(thiophen-2-yl)pyrimidin-2-amine (8d): m.p. 208-210 °C; IR (KBr, ν_{max}, cm^{-1}): 3462 (NH_2), 1445 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.03 (s, 2H, NH_2), 8.05 (s, 1H, $H_{pyrimidin}$), 7.31-8.09 (m, 8HAr); ^{13}C NMR δ: 94.70, 127.33, 127.67, 128.56, 128.81, 130.91, 133.80, 135.62, 136.21, 142.50, 160.74, 162.74, 164.02; MS: (%) 253 (M^+, 90). Calcd. % $C_{14}H_{11}N_3S$: C, 69.65;H 3.53;N, 14.85; Found: C, 69.08; H, 3.16; N, 14.10.

RESULTS AND DISCUSSION

Chalcones (**3a-d**) for heterocyclic compounds synthesis were prepared by base catalyzed condensation of 2-acetylthiophene ketone (**1**) with appropriately substituted benzaldehydes (**2**). The synthetic routes to our prepared compounds are shown in (**Scheme-I**, Table-1).

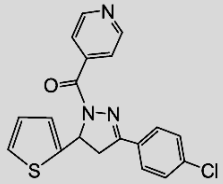
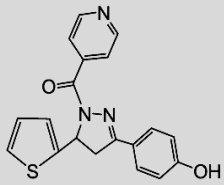
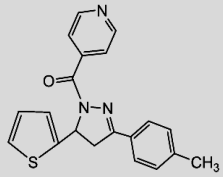
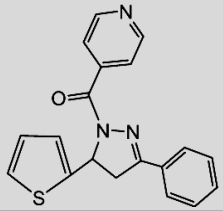
TABLE-1
CHALCONES (**3**) DERIVATIVES

Compound	R	Yield (%)*
3a	Cl	98
3b	OH	96
3c	CH_3	94
3d	H	91

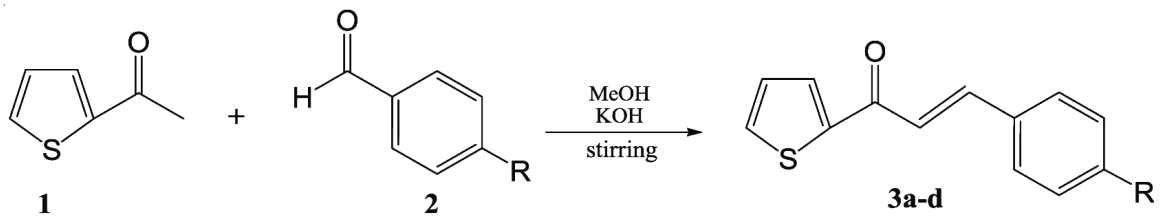
*Isolated yield

Pyrazoles (**5a-5d**) were respectively obtained from the reactions of each of chalcones (**3a-3d**) with isoniazid (**4**). These reactions immediately cyclized to give a pyrazole ring under microwave irradiation (**Scheme-II**, Table-2).

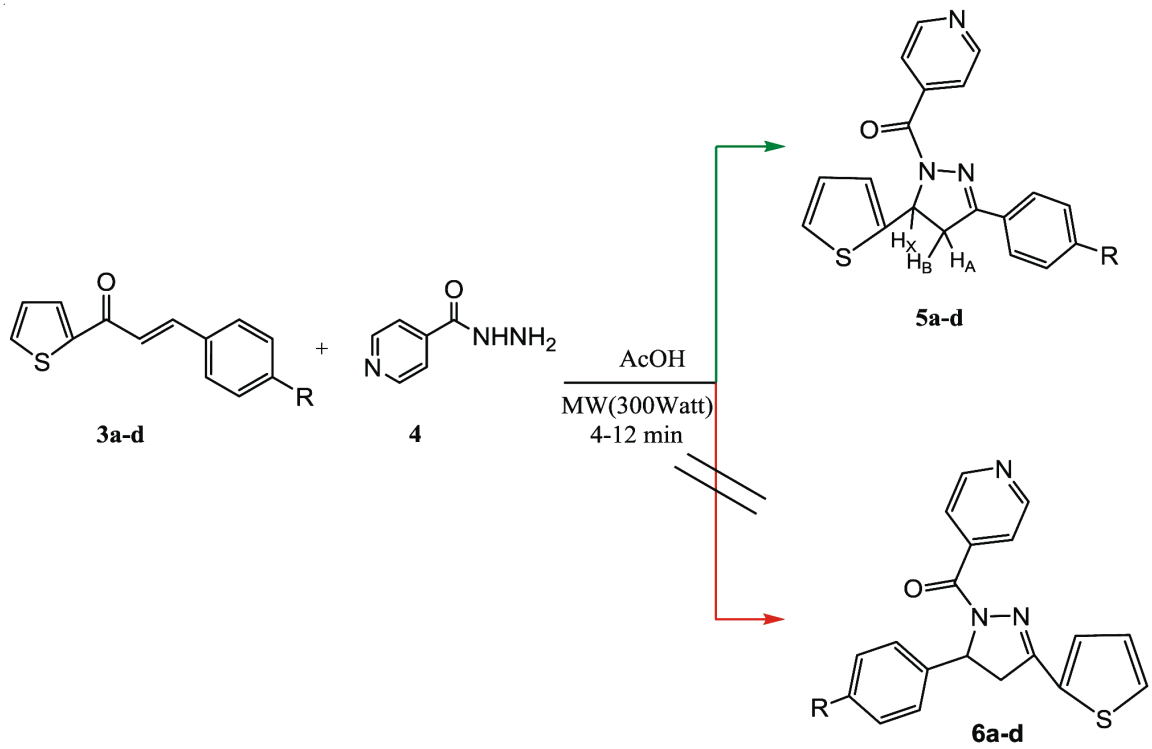
TABLE-2
SYNTHESIS OF PYRAZOLES FROM ISONIAZID

Compound		Microwave irradiation		Conventional method	
		Time (min)	Yield (%)*	Time (h)	Yield (%)*
5a		7	79	4.0	46
5b		4	84	3.5	44
5c		11	81	5.5	43
5d		12	77	7.0	49

*Isolated yield



Scheme-I: Synthesis of chalcones (**3a-d**)



Scheme-II: Regiospecific synthesis of pyrazoles (**5a-d**)

Based on the elemental analysis results and spectroscopic data from the isolated products, the product could be one of the two possible isomers **5** or **6** (**Scheme-II**). **Scheme-II** show that the product may be one of the two possible isomers **5** or **6**.

Through our research in previously studies[14,15] for identical reactions depends on 1D NMR spectroscopy, in our opinion we cannot depend on 1D NMR to decide which isomer formed. Therefore, we studied here facile and highly efficient 2D NMR experiment to determine the structure of the isomer. The present work provides unambiguous evidence of the obtained pyrazoles on the basis of the long-range C-H connectivity's *via* ^{1}H-^{13}C HMBC in which it used to study ^{2}J and ^{3}J correlations between ^{13}C and ^{1}H, multiple bonds away that can shows connectivity with through nuclei without attached protons. Fig. 1a show the full spectrum of ^{1}H-^{13}C HMBC for isolated product **5a** or **6a**, depend on the number of correlations between the H-pyrazole toward carbons that are five and six bonds away (Fig. 1b). Being of five correlations in 2D NMR spectrum of the isolated product is prove conclusively for the proposed structure **5a** (Fig. 1c). Therefore, formation of pyrazole isomers (**5a-d**) is assumed to be formed *via* the above green path illustrated in **Scheme-II**.

Pyrimidine compounds (**8a-8d**) show the IR spectra absorbance for amino group at about 3440 cm^{-1} and C=N at 1450 cm^{-1}. Their ^{1}H NMR spectra are characterized by the presence of a singlet for two protons at about δ = 7.0 ppm is assigned to the amino protons.The singlet for $H_{\text{pyrimidin}}$ is observed at about δ = 8.05 ppm (**Scheme-III**, Table-3).

Finally, the structure of products (**8a-d**) was ascertained utilizing X-ray diffraction.

Conclusion

A simple and efficient microwave irradiation protocol was developed for the synthesis of pyrazoles and pyrimidines with

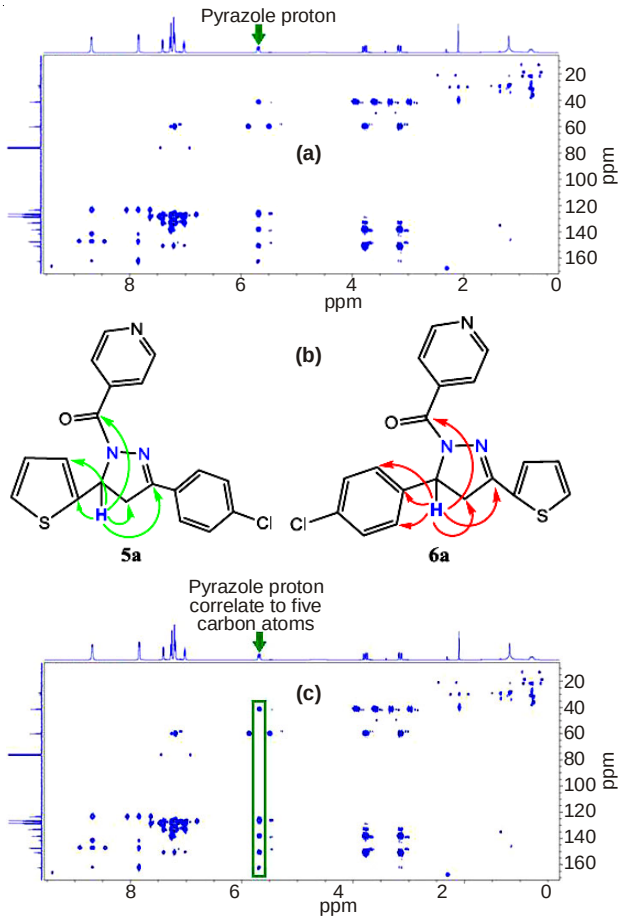
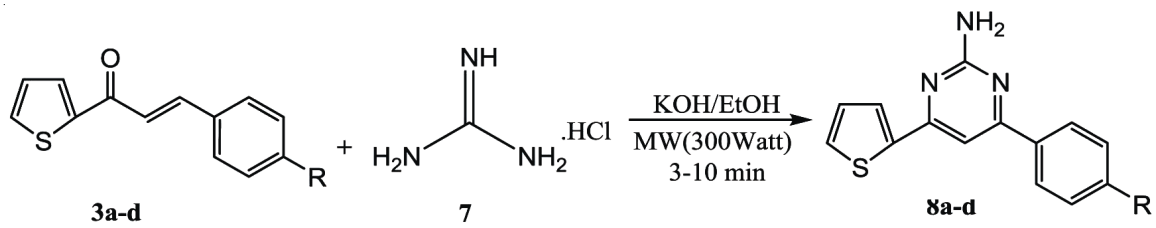
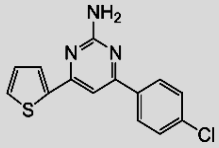
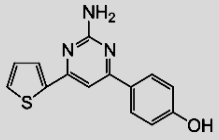
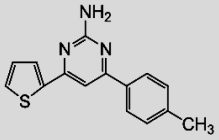
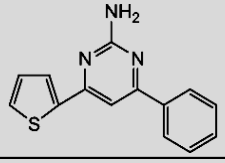


Fig. 1. (a) 2D-HMBC NMR of the compound **5a** or **6a** and assignment for pyrazole proton (b) Number of correlations between pyrazole proton toward carbons in the possible regiospecific products **5a** and **6a**; (c) number of correlation between pyrazole proton and carbon atoms



Scheme-III: Synthesis of pyrimidines (**8a-d**)

TABLE-3
SYNTHESIS OF PYRIMIDINE FROM GUANIDINE HYDROCHLORIDE

Compound		Microwave irradiation		Conventional method	
		Time (min)	Yield (%)*	Time (h)	Yield (%)*
8a		3	78	4	48
8b		9	74	7	53
8c		5	78	6	50
8d		10	75	7	51

*Isolated yield

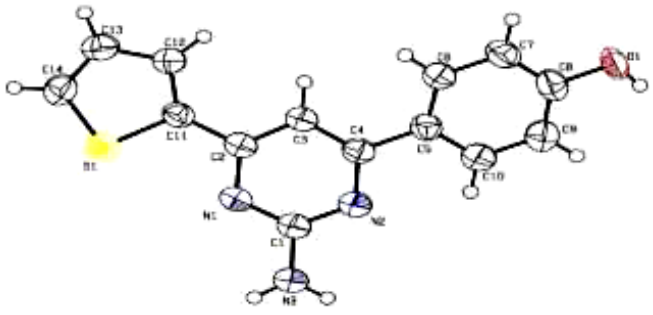


Fig. 2. X-ray crystal structure of the compound **8b**

high yields and short reaction times. Structural identification of the pyrazoles and pyrimidines was achieved using 2D HMBC NMR and single-crystal X-ray diffraction.

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