New One Step Synthesis of 3,5-Disubstituted Pyrazoles under Microwave Irradiation and Classical Heating

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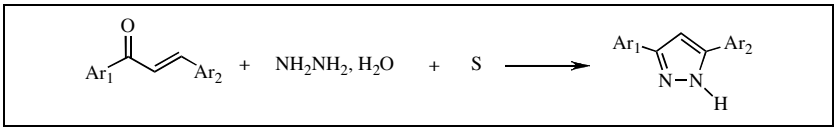

A convenient one pot procedure for the synthesis of 3,5-disubstituted pyrazoles by condensation of chalcones, hydrazine hydrate and sulfur in ethanol under microwave irradiation and conventional heating method is reported. The hydrogen sulfide is produced during the reaction. The pyrazoles are obtained in good yields and excellent state of purity. The structures of new compounds were confirmed by IR, ^{1}H, and ^{13}C NMR, MS and elemental analysis.

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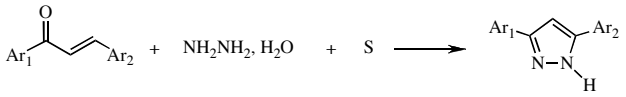
INTRODUCTION

The synthesis of pyrazoles remains of great interest because they constitute an important class in pharmaceutical and agrochemical industry [1]. The 3,5-Disubstituted pyrazoles have displayed a wide range of biological activities such as in inhibiting lung cancer cell growth [2,3]. For many years, numerous methods have been developed in order to synthesize this class of heterocycles [4]. Very little is known concerning the synthesis of pyrazoles using chalcones as starting compounds [5]. The synthesis of 3,5-disubstituted pyrazoles by condensation of 1,3-diketones with hydrazine or its derivatives is the most widely used method [6], but unfortunately this condensation leads to the formation of undesired isomers as major components [7-9]. As a part of a program directed to obtain 3,5-disubstituted pyrazole molecules which can be used as corrosion inhibitors and organic ligands in coordination chemistry [10,11], we have particularly developed a simple new one step synthesis of the 3,5-disubstited pyrazoles from chalcones with hydrazine hydrate in the presence of sulfur (Scheme 1. We have compared the results obtained by microwave irradiation and conventional heating. This reaction was easily achieved by microwave irradiation and the pyrazoles are obtained in good yields and excellent state of purity. The chalcones used are either commercialized products or quickly prepared by a general procedure [12]. The application of microwave in organic synthesis for conducting reactions at highly accelerated rates is an emerging technique [13]. In recent years, the use of microwave energy has become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and improving yields, as well as to produce new reactions [14]. This technique has been applied with success to a number of synthesis of heterocylic compounds proceeding with or without solvent such as 1,2,4-triazoles [15,16], 1,3,4-oxadiazoles [17] and 1,3,4-thiadiazoles [18,19].

Scheme 1



1, 2a	$Ar_1 = C_6H_5$	$Ar_2 = C_6H_5$
b	$Ar_1 = 4\text{-}CH_3OC_6H_4$	$Ar_2 = 4\text{-}CH_3OC_6H_4$
c	$Ar_1 = 4\text{-}CH_3C_6H_4$	$Ar_2 = 4\text{-}CH_3C_6H_4$
d	$Ar_1 = 4\text{-}CH_3C_6H_4$	$Ar_2 = 4\text{-}ClC_6H_4$
e	$Ar_1 = 4\text{-}CH_3C_6H_4$	$Ar_2 = C_6H_5$
f	$Ar_1 = 4\text{-}ClC_6H_4$	$Ar_2 = 4\text{-}ClC_6H_4$
g	$Ar_1 = 4\text{-}FC_6H_4$	$Ar_2 = 4\text{-}FC_6H_4$
h	$Ar_1 = 4\text{-}CH_3OC_6H_4$	$Ar_2 = 4\text{-}FC_6H_4$
i	$Ar_1 = 4\text{-}FC_6H_4$	$Ar_2 = 4\text{-}ClC_6H_4$
j	$Ar_1 = 4\text{-}NO_2C_6H_4$	$Ar_2 = 4\text{-}NO_2C_6H_4$

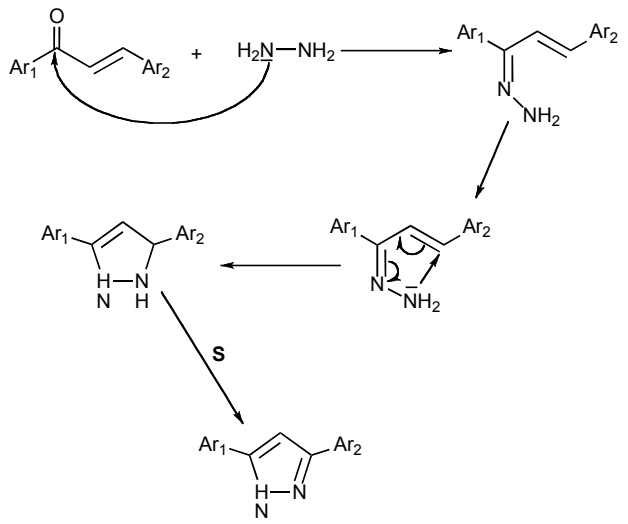
RESULTS AND DISCUSSION

The 3,5-disubstituted pyrazoles prepared from chalcones by the action of hydrazine in presence of sulfur are obtained in good yield. We have compared the speeds of reactions performed under microwave irradiation with those performed under classical heating. The results show that for products **2a-j**, the microwave irradiation appeared to be more rapid, indeed, after 2 h of microwave heating, the compounds **2a-j** can be obtained in excellent yields and good purity whereas with conventional heating, 15 h were required. The reaction between chalcones and hydrazine leads first to the formation of the corresponding

dihydropyrazoles. This latter is rapidly dehydrogenated by sulfur (Scheme 2). The hydrogen sulfide is produced during this reaction.

The elemental analysis (Table) and mass spectra are in accordance with the proposed structures of new pyrazole derivatives. The melting points of the already known pyrazoles agree with those reported in the literature (Table). The IR, ^1H and ^{13}C nmr data are given.

Scheme 2



EXPERIMENTAL

Melting points were determined on an IA 9000 series Electrothermal apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer a Spectrum One FTIR Spectrometer (values in cm^{-1}). ^1H and ^{13}C nmr spectra were recorded on a Bruker F.T. AC 300 spectrometer (300 MHz for ^1H nmr and 75 MHz for ^{13}C nmr) using dimethyl-d_6 sulfoxide (DMSO) solvent. Matrix assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the pyrazole compounds. All starting materials were of reagent grade and used as purchased.

General Procedure for the Synthesis of 3.5-disubstituted pyrazoles (2a-j).

Microwave irradiation method. A mixture of chalcones (**1a-j**) (0.02 mole), sulfur (0.03 mole) and hydrazine monohydrate (0.04 mole) in ethanol (20 ml) was introduced into a fluoropolymere cylindrical flask placed in a MARS5 XP-1500 PLUS CEM multimode microwave reactor and irradiated (300 W) for 2 h at 150°C under pressure. After cooling, the solvent was evaporated under reduced pressure. The hydrogen sulfide was trapped using liquid nitrogen. The residue was treated with ethanol or ethyl acetate and filtered to remove the excess of sulfur. The solid compound is collected by filtration and dried.

Classical heating method. The mixture of chalcones (**1a-j**) (0.05 mole), sulfur (0.07 mole) and hydrazine monohydrate (0.1 mole) in ethanol (50 ml) was introduced into a steel autoclave. The resulting mixture was heated to 140°C for 15 hours with vigorous stirring. After cooling, the residue was treated in the same procedure as described above.

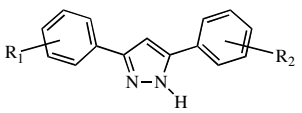
Table

Physical and Analytical Data of 3,5-Disubstuted Pyrazoles **2a-j**.

Compound No.	Ar_1	Ar_2	Yield (%)		Mp (°C)	Molecular Formula	Analysis % Calcd./Found		
			MW	Heating			C	H	N
2a	C_6H_5	C_6H_5	87	83	199	$C_{15}H_{12}N_2$	81.79	5.49	12.72
					[20,21]		81.57	5.72	12.48
2b	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	94	91	172	$C_{17}H_{16}N_2O_2$	72.84	5.75	9.99
					[22]		72.91	5.98	10.37
2c	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	89	83	234	$C_{17}H_{16}N_2$	82.22	6.49	11.28
							82.34	6.61	11.24
2d	4-$CH_3C_6H_4$	4-ClC_6H_4	92	91	212	$C_{16}H_{13}Cl\,N_2$	71.51	4.88	10.42
					[21]		71.54	4.67	10.28
2e	4-$CH_3C_6H_4$	C_6H_5	90	82	175	$C_{16}H_{14}N_2$	82.02	6.02	11.96
							82.17	5.98	12.01
2f	4-ClC_6H_4	4-ClC_6H_4	78	70	241	$C_{15}H_{10}Cl_2N_2$	62.31	3.49	9.69
					[21]		62.63	3.42	9.45
2g	4-FC_6H_4	4-FC_6H_4	75	68	210	$C_{15}H_{10}F_2N_2$	70.31	3.93	10.93
					[22]		70.55	3.87	10.89
2h	4-$OCH_3C_6H_4$	4-FC_6H_4	82	61	182	$C_{16}H_{13}FN_2O$	71.63	4.88	10.44
							71.34	4.93	10.69
2i	4-FC_6H_4	4-ClC_6H_4	79	75	220-222	$C_{15}H_{10}ClFN_2$	66.06	3.70	10.27
					[21]		65.96	3.52	10.35
2j	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	63	55	266-268	$C_{15}H_{10}N_4O_4$	58.07	3.25	18.06
					[22]		58.10	3.33	18.17

IR, ^{1}H, and ^{13}C nmr, MS and elemental analysis. Data are in accordance with the proposed structures, are given below.

The general formula of the parent pyrazoles (**2a-j**) is given below:



3,5-Diphenyl-1*H*-pyrazole (**2a**). ir (cm^{-1}) : 3137, 3085, 2987, 2841, 1888, 1606, 1486, 1308, 1087, 971, 828, 769. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 7.01 (s, 1H), 7.37-7.43 (m, 6H); 7.66-7.70 (m, 4H), 13.38 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 99.60, 125.07, 127.77, 128.81, 129.40, 133.52, 144.2 MALDI-TOFMS: *m/z* 221 (M +1).

3,5-Bis(4-methoxyphenyl)-1*H*-pyrazole (**2b**). ir (cm^{-1}) : 3320, 3210, 2961,2836, 1188, 1608, 1572, 1530, 1240, 1173, 1020, 833, 789. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 3.85 (s, 6H) OCH_3; 6.95 (s, 1H); 7.00 (d, 4H, J = 8.4); 7.71 (d, 4H, J = 8.4), 13.34 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 55.47, 98.30, 116.30, 126.97, 128.40, 146.44, 162.97. MALDI-TOFMS: *m/z* 281 (M +1).

3,5-Bis(4-methylphenyl)-1*H*-pyrazole (**2c**). ir (cm^{-1}) : 3111, 3018, 2914, 2905, 2851, 1882, 1609, 1502, 1458, 1170, 968, 813, 764. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 2.32 (s, 6H) CH_3; 7.07 (s, 1H); 7.25 (d, 4H, J = 7.9); 7.71 (d, 4H, J = 7.9), 13.25 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 20.79, 98.91, 124.95, 127.16, 129.30, 131.51, 136.24, 145.38. MALDI-TOFMS: *m/z* 249 (M +1).

3-(4-Chlorophenyl)-5-(4-methylphenyl)-1*H*-pyrazole (**2d**). ir (cm^{-1}) : 3111, 2992, 2909, 2846, 1880, 1613, 1502, 1466, 1442, 1168, 968, 821, 769. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 2.33 (s, 3H) CH_3; 7.16 (s, 1H); 7.49-7.51 (d, 4H, J = 8.2); 7.80-7.84 (d, 4H, J = 8.2), 13.37 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 20.79, 99.48, 124.99, 126.71, 128.74, 129,39, 132.03, 137.29, 143.90 MALDI-TOFMS: *m/z* 269, 270, 271 (M +1).

3-(4-Methylphenyl)-5-(4-phenyl)-1*H*-pyrazole (**2e**). ir (cm^{-1}) : 3111, 3018, 2987, 2909, 2849, 1880, 1603, 1502, 1461, 1179, 971, 831, 769. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 2.33 (s, 3H) CH_3; 7.13 (s, 1H); 7.28-7.36 (m, 5H); 7.77 (d, 4H, J = 7.9), 13.30 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 14.52, 92.97, 118.75, 121.39, 122.47, 123.06, 130.81, 146.25 MALDI-TOFMS: *m/z* 235 (M +1)

3,5-Bis(4-chlorophenyl)-1*H*-pyrazole (**2f**). ir (cm^{-1}) : 3139, 3105, 2853, 1888, 1610, 1492, 1230, 1156, 970, 825, 767. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 7.17 (s, 1H); 7.41-7.47 (d, 4H, J = 7.4); 8.05-8.11 (d, 4H, J = 7.4), 13.34 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 99.90, 126.39, 128.71, 130.74, 137,39, 147,23 MALDI-TOFMS: *m/z* 289, 290, 291, 292, 293 (M +1).

3,5-Bis(4-fluorophenyl)-1*H*-pyrazole (**2g**). ir (cm^{-1}) : 3142, 3002, 2857, 1598, 1515, 1328, 1308, 1108, 973, 852, 751, 678. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 7.21 (s, 1H); 7.49-7.53 (m, 4H); 7.82-7.85 (d, 4H, J = 7.0), 13.35 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 98.54, 123.60, 125.71, 128.09, 132.29, 135.48, 144.82 MALDI-TOFMS: *m/z* 257 (M +1).

3-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (**2h**). ir (cm^{-1}) : 3107, 2991, 2913, 2843, 1610, 1486, 1518, 1492, 1305, 1282, 1080, 973, 852, 753, 680. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 3.79 (s, 3H) OCH_3; 6.95 (s,1H), 7.16 (d, 2H, J = 7.63 Hz); 7.45-7.59 (m, 6H), 13.34 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 55.43, 99.57, 115.23, 123.92, 125.23, 128.68, 132.33, 136.08, 142.94 MALDI-TOFMS: *m/z* 269 (M +1).

3-(4-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrazole (**2i**). ir (cm^{-1}) : 3140, 3101, 2919, 2851, 1884, 1611, 1502, 1448, 1227, 1093, 826, 784. ^{1}H nmr (DMSO-d$_6$) : δ (ppm) 7.22 (s,1H),7.50-7.54 (m, 4H); 7.83-7.86 (d, 4H, J = 7.1), 13.36 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 102.15, 114.83, 126.49, 129.73, 149.38. MALDI-TOFMS: *m/z* 273, 274, 275 (M +1).

3,5-Bis(4-nitrophenyl)-1*H*-pyrazole (**2j**). ir (cm^{-1}): 3147, 3085, 2987, 2841, 1888, 1605, 1572, 1505, 1492, 1400 1328, 1302, 1240, 1111, 971, 833, 757. ^{1}H nmr (DMSO-d$_6$): δ (ppm) 6.88 (s,1H); 7.18(d, J = 8.54 Hz, 4H); 7.76 (d, 4H, J = 8.54 Hz), 13.35 (s, 1H). ^{13}C nmr (DMSO-d$_6$): δ (ppm) 100.01, 124.18, 125.63, 128.13, 130.02, 137.90, 148.41. MALDI-TOFMS: *m/z* 311 (M +1).

REFERENCES AND NOTES

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