A Comparative Study on the Synthesis of 4-Alkyl-1,3-diarylpyrazoles Using Microwave Irradiation and Conventional Thermal Methods

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A convenient synthesis of 4-alkyl-1,3-diarylpyrazoles (**2**) under microwave irradiation as well as conventional thermal method using Vilsmeier cyclization is reported. Microwave irradiation has resulted in the reduction of time from hours to seconds.

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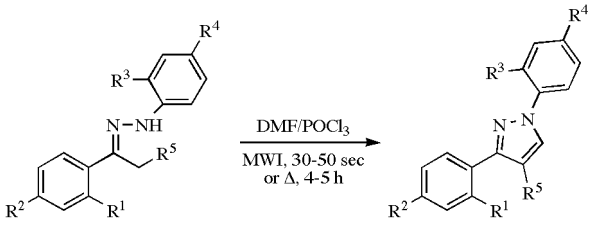
Introduction.

There has been a growing interest in the use of microwave irradiation in organic synthesis during the past decade, since the first contribution by Gedye *et al* [1] and Giguere *et al* [2] in 1986. The number of publications and reviews that have advocated the advantages and the use of microwave irradiation over conventional technology have increased significantly [3]. Remarkable decreases in reaction time and, in some cases, cleaner reaction and better yields have made this technique widely applicable in organic synthesis.

Pyrazole derivatives are principally used in medicine and have enormous potential as pharmaceutical agents due to their biological activities such as endocrinological, anti-inflammatory and anti-hyperglycemic [4]. Though many syntheses have been developed for pyrazole derivatives, due to their great importance, designing facile synthetic routes remains an active research area [5]. A number of reports have been published from our lab on the use of Vilsmeier reagent as an effective intramolecular cyclizing tool and a number of heterocyclic compounds have been synthesized [6]. We thought it is worth attempting the synthesis of pyrazole derivatives by exploiting microwave irradiation and the Vilsmeier reagent. However, there are few examples of the preparation of the title compounds from α-alkylacetophenone phenylhydrazones in the literature [7]. Here, we describe our results on the synthesis of pyrazoles using microwave irradiation.

Results and Discussion.

Scheme



1a-i **2a-i**

MWI: Microwave irradiation; Δ: Thermal Method

α-Alkylacetophenone phenylhydrazones in DMF was subjected to Vilsmeier reaction with three equivalents of DMF/$POC1_3$ *duo*. After 10 min at room temperature, the content of the flask was subjected to microwave irradiation for 30 to 50 sec at 30% power (210 W). The creamy yellow precipitate obtained was found to be 4-alkyl-1,3-diarylpyrazoles **2** after usual work-up and chromatographic purification. The same compounds were also synthesized by conventional heating method for comparison. In conventional heating method, after the addition of $POC1_3$, the reaction mixture was heated on an oil bath at 90 °C for 4-5 h. The reaction yielded the same pyrazoles with slight variation in the yield. In the case of 2-hydroxypropiophenone phenylhydrazone, the product **2i** was obtained by stirring the reaction mixture at room temperature, without heating. The results are summarized in table.

Table

Synthesis of 4-Alkyl-1,3-diarylpyrazoles

Product	Substituents					Time		Yield (%)		
	R^1	R^2	R^3	R^4	R^5	MWI (sec)	Δ[a] (hrs)	MWI	Δ	m.p. (°C)
2a	H	H	NO_2	NO_2	CH_3	35	4.5	78	76	140
2b	H	H	NO_2	NO_2	C_2H_5	45	4.0	65	56	136
2c	H	H	H	NO_2	CH_3	50	5.0	70	67	145
2d	H	H	H	NO_2	C_2H_5	50	5.0	49	52	149
2e	H	CH_3	NO_2	NO_2	CH_3	40	4.0	74	76	158
2f	H	CH_3	NO_2	NO_2	C_2H_5	45	5.0	61	65	166
2g	H	CH_3	H	NO_2	CH_3	47	5.0	68	63	170
2h	H	CH_3	H	NO_2	C_2H_5	40	4.5	45	41	174
2i	OH	H	NO_2	NO_2	CH_3	45	5.0[b]	60	57	166

[a] The reaction was carried at 90 °C; [b] The reaction was carried out at room temperature.

Pawar and Bose [7] have reported a one-pot synthesis of 4-alkyl substituted pyrazoles. They have synthesized 4-alkyl-1,3-diarylpyrazoles starting from unsubstituted phenylhydrazones of 2-acyl-5-chlorophenols under thermal conditions. We carried out reaction without hydroxyl group on the α-alkylacetophenone part and strong electron withdrawing nitro groups on the phenylhydrazine moiety. The reaction proceeded smoothly yielding uncomplicated

products. Therefore a hydroxyl group at the 2-position is not essential and the presence of electron withdrawing does not affect the reaction. The use of microwave irradiation has drastically reduced the reaction time from several hours to a few seconds with good yields.

In conclusion, we have disclosed a one-pot efficient microwave assisted synthesis of 4-alkyl-1,3-diarylpyrazoles in moderate to good yields from α-alkylacetophenone phenylhydrazones *via* Vilsmeier cyclization. In this method, the reaction time has been brought down from hours to seconds compared to conventional heating method. Its broad scope as well as the easy access to the starting materials and short reaction time under microwave irradiation should make this methodology widely applicable in organic synthesis.

EXPERIMENTAL

Melting points were uncorrected. Infrared spectra were recorded as KBr pellets on a Nicolet Impact 400 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHzand at 75 MHz respectively, using $CDC1_3$ solvent with TMS as the internal standard. Mass spectra were obtained on a Hewlett Packard 5890 Series II with an HP 5971A mass selective detector.

General Procedure for the Preparation of 4-Alkyl-1,3-diarylpyrazoles (**2**) Under Conventional Heating Method.

α-Alkylacetophenone phenylhydrazones **1a-h** (0.005 mol) was dissolved in 8 mL DMF, cooled to 0 °C and 1.4 mL of $POC1_3$, was added dropwise over 10 min. The reaction mixture was then heated at 90 °C for 4-5 h. The contents of the flask were poured into crushed ice and left in the refrigerator overnight. The product obtained was collected by filtration, washed with water and dried. This crude material was purified by column chromatography using 60 - 120 silica gel and petroleum ether-ethyl acetate (80:20) solvent system as eluent to afford **2a-h**. In the case of **2i**, the reaction mixture was stirred at room temperature for 5 h.

General Procedure for the Preparation of 4-Alkyl-1,3-diarylpyrazoles (**2**) Under Microwave Irradiation Method.

α-Alkylacetophenone phenylhydrazones **1a-h** (0.005 mol) was dissolved in 8 mL DMF, cooled to 0 °C and 1.4 mL of $POC1_3$, was added drop wise over 10 min. Then the reaction mixture was subjected to microwave irradiation for 30 - 50 sec at 30% power (210 W). After the usual work-up, the crude product was purified by column chromatography.

1-(2,4-Dinitrophenyl)-4-methyl-3-phenylpyrazole (**2a**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.61 (s, 1H), 8.43 (d, J = 9.3 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 7.36 - 7.45 (m, 3H) 2.31 (s, 3H); ^{13}C NMR (75 MHz $CDC1_3$): δ 154.80, 144.58, 142.26, 136.98, 132.11, 129.08, 128.45, 127.63, 127.23, 124.26, 121.13, 119.29, 10.29; IR (KBr) 1603, 1553, 1520, 1336; MS *m/z* 324 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60,44; H, 3.98; N, 16.32.

1-(2, 4-Dinitrophenyl)-4-ethyl-3-phenylpyrazole (**2b**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.63 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.64 (t, J= 7.2 Hz), 7.62 (s, 1H) 7.34-7.44 (m, 3H), 2.73 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDC1_3$) 157.36, 154.39, 144,59, 137.11, 132.25, 128.56, 127.75, 127.19, 126.48, 124.28 121.15, 18.19, 14.13; IR(KBr) 3091, 3065, 1605, 1547; MS m/z 338 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56; Found: C, 60.44; H, 3.98; N, 16.32.

4-Methyl-1-(4-Nitrophenyl)-3-phenylpyrazole (**2c**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz,$CDC1_3$): δ 8.29 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.85 (s, 1H), 7.77 (d, J = 7.1 Hz, 2H) 7.36-7.48 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDC1_3$): δ 154.51, 144.86, 144.27, 132.82, 128.55 128.24, 127.59, 127.02, 125.32, 118.33, 117.73, 10.26; IR (KBr) 1596, 1509, 1330, 1308; MS m/z 279 (M^+).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69, N, 15.04. Found: C, 68.37; H, 4.54; N, 15.31.

4-Ethyl-1-(4-nitrophenyl)-3-phenylpyrazole (**2d**).

This compound was obtained as a yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.30 (d, J = 8.9Hz, 2H) 7.88 (d, J = 8.9Hz, 2H) 7.86 (s.1H) 7.73 (d, J = 7.4 Hz, 2H) 7.88 (d, J = 8.9 Hz, 2H), 7.86 (s.1H), 7.73 (d, J = 7.4 Hz, 2H), 7.36-7.47 (m, 3H) 2.33 (q, J = 7.4 Hz, 2H) 1.28 (t, J = 7.4 Hz, 3H); ^{13} C NMR (75 MHz, $CDC1_3$) 153.15, 144.37, 144.24, 132.99, 128.56, 128.29, 127.79, 125.75, 125.57, 125.33, 117.78, 18, 17, 14.38; IR (KBr) 3063, 2964, 2926, 1593, 1512; MS *m/z* 293 (M^+).

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.87; H, 5.04; N, 14.12.

1-(2,4-Dinitrophenyl)-4-methyl-3-(4-methylphenyl)pyrazole (**2e**).

This compound was obtained as a pale yellow crystalline solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 9.00 (s, 1H), 8.44 (d, J = 9.0 Hz, 1H), 7.82 (d, J=9.0 Hz, 1H), 7.60(s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9Hz 2H), 2.37 (s, 3H), 2.29(s, 3H); ^{13}C NMR (75 MHz, $CDC1_3$: δ 161.59, 154.75, 138.41, 136.88, 129.60,129.38, 128.45, 126.42, 126.84, 126.28, 124.11, 114.10, 104.47, 21.13, 10.16; IR (KBr) 1602, 1552, 1523, 1359, 1245; MS *m/z* 338 (M^+).

Anal. Calcd**.** for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.12; H, 4.31; N, 16.72.

1-(2,4-Dinitrophenyl)-4-ethyl-3-(4-methylphenyl)pyrazole (**2f**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.62 (s, 1H), 8.43 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H) 7.59 (s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 2.71 (q, J = 7.4 Hz, 2H), 2.37(s, 3H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDC1_3$): δ 154.48, 144.48, 138.59, 137.16, 129.40, 129.30, 127.69, 127.62, 127.19, 126.46, 124.20, 121, 19, 21.31, 18.26, 14.13; IR (KBr) 3054, 2942, 1531; MS *m/z* 352 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.12; H, 4.74; N, 16.15.

4-Methyl-3-(4-methylphenyl)-1-(4-nitrophenyl)pyrazole (**2g**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.32 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4

Hz, 2H), 7.62 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H), 2.28(s, 3H); ^{13}C NMR (75 MHz, $CDC1_3$): δ 8 155.34, 150.40, 145.39, 136.11, 131.48, 129.42, 125.71, 122.49, 120.45, 118.32, 113.23, 20.44, 11.92; IR (KBr) 1605, 1543, 1510, 1342, MS m/z 293 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5,15; N, 14.32. Found: C, 69.32; H, 5.29; N, 14.49.

4-Ethyl-3-(4-methylphenyl)-1-(4-nitrophenyl)pyrazole (**2h**).

This compound was obtained as a yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.45 (d, J = 8.4, Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.65(s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 2.84 (q, J = 6.9 Hz, 2H), 2.42 (s, 3H), 1.23 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDC1_3$): δ 154.92, 150.72, 147.35, 135.72, 132.59, 128.83, 126.42, 122.75, 120.54, 119.34, 114.79, 21.63, 19.30, 14.07, IR (KBr) 3061, 2954, 1604, 1542; MS *m/z* 307 (M^+).

Anal. Calcd. for $C_8H_{17}N_3O_3$: C, 70.34, H, 5.57; N, 13.67. Found C, 70.11; H, 5.43; N, 13.92.

1-(2,4-Dinitrophenyl)-3-(2-hydroxyphenyl)-4-methylpyrazole (**2i**).

This compound was obtained as a pale yellow solid; ^{1}H NMR (300 MHz, $CDC1_3$): δ 9.68 (s, 1H), 8.72 (s, 1H), 8.51 (d, J = 11.1 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.61 (s, 1H), 7.28 (m, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 2.41(s, 3H); ^{13}C NMR (75 MHz, $CDC1_3$): δ 156.01, 153.21, 145.80, 137.20, 136.13, 130.43, 129.97, 127.72, 124.92, 121.26, 121.06, 119.74, 119.39, 117.49, 116.17, 11.52; IR (KBr) 3320, 1685, 1600, 1538, MS *m/z* 340 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4O_5$: C, 56.47; H 3.55, N, 16.46. Found: C, 56.02; H, 3.42; N, 16.74.

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