

Microwave-Assisted Synthesis of Some 3,5-Arylated 2-Pyrazolines

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Abstract: Condensation of 2-acetylnaphthalene with benzaldehydes under microwave irradiation affords chalcones which undergo facile and clean cyclizations with hydrazines RNHNH₂ (R= H, Ph, Ac) to afford 3,5-arylated 2-pyrazolines in quantitative yields, also under microwave irradiation and in the presence of dry AcOH as cyclizing agent. The results obtained indicate that, unlike classical heating, microwave irradiation results in higher yields, shorter reaction times (2-12 min.) and cleaner reactions.

Keywords: Microwave irradiation; chalcones; 3,5-arylated-2-pyrazolines; pyrazolines; heterocyclic synthesis.

Introduction

Variously substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class. In particular, they are used as antitumor [1], antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents [2-10]. Some of these compounds have also anti-inflammatory, anti-diabetic, anaesthetic and analgesic properties [11-14]. Moreover, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively as useful synthons in organic synthesis [15-19]. A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of

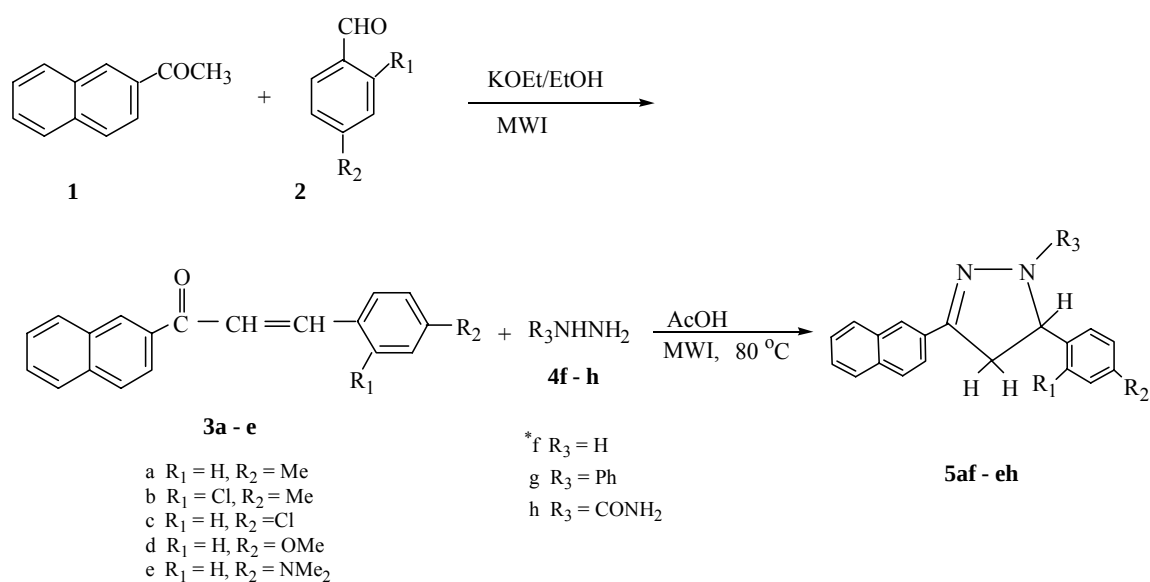
aromatic ketones and aldehydes to give α,β -unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines [11, 20-22]. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-pyrazolines in the presence of a suitable cyclizing reagent like acetic acid [23,24].

In recent years, a significant portion of research in heterocyclic chemistry has been devoted to 2-pyrazolines containing different aryl groups as substituents, as evident from the literature [25-33]. We have recently reported on the synthesis of some newly 3,5-naphthylated 2-pyrazolines which exhibit efficient antimicrobial activity against a variety of test organisms [8].

Results and Discussion

As a result of our studies related to the development of synthetic protocols using microwave irradiation, we now report a novel and easy access to 3,5-arylated 2-pyrazolines using a one-pot procedure and demonstrate its superiority over our previously reported classical heating method [8]. We report in this paper some aldol condensation reactions between 2-acetylnaphthalene (**1**) and benzaldehydes **2a-e** in the presence of $\text{KOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH}$ to give intermediate chalcones **3a-e** which undergo a rapid cyclization with hydrazines **4f-h** under microwave irradiation at 80°C to yield 2-pyrazolines **5af-eh** quantitatively in 2-12 minutes (Scheme 1). The heterocyclic products were characterized on the basis of their IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, MS spectral and elemental analysis (Table 2).

Scheme 1



* Acetylation, in situ, occurs in the presence of AcOH to convert the initially formed 2-pyrazolines ($\text{R}_3 = \text{H}$) mainly into their acetylated derivatives ($\text{R}_3 = \text{COCH}_3$).

Conclusions

In summary, this work demonstrates a rapid, efficient and environmentally friendly method of synthesis of 3,5-arylated 2-pyrazolines under microwave heating, and the results obtained confirm the superiority of the microwave irradiation method over the classical heating one.

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Experimental

General

All melting points were determined on a Büchi 530 melting point apparatus, and are uncorrected. The ^1H -NMR spectra were recorded for deuteriochloroform solutions using tetramethylsilane as the internal standard on Jeol FX (at 90 MHz) and Brüker AM (at 200 MHz) spectrometers at ambient temperature. IR spectra were recorded on a Shimadzu IR-435U-04 instrument using potassium bromide pellets. Elemental analyses were performed at the Iran Polymer Research Center, Karaj, Iran.

General procedure for microwave-assisted preparation of 3,5-diaryl-2-pyrazoline derivatives (5af-eh).

In the first step the chalcones **3a-e** are prepared by the reaction between 2-acetylnaphthalene (1.70 g, 10 mmol), dissolved in 1M $\text{KOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH}$ solution (10 mL), and the corresponding benzaldehyde (10 mmol) under microwave irradiation (300 watt) for a few min. The resulting crude yellow solid is filtered, washed successively with dilute HCl solution and distilled water and finally recrystallized from ethanol (95%) to give the pure chalcones **3a-e** in 80-95 % yield. In the second step, the hydrazine reagent (12 mmol) is then added dropwise to a stirring solution of the chalcones **3a-e** (10 mmol) in glacial AcOH (10 mL). The mixture is subjected to microwave heating for several min. using a domestic microwave oven (300 watt) to afford 2-pyrazolines, which were recrystallized from ethanol (95%) to give pure compounds **5af-eh** with a 82-99% yield. Analytical data for the prepared compounds is given in Table 1. Spectroscopic data is summarized in Table 2.

Table 1. Microwave synthesis of 3,5-arylated 2-pyrazolines (**5af-e**) (power = 300 W)

Compound	Molecular Formula	Irradiation Time (min)	Yield ^a (%)	M.P. (°C)	Elemental Analysis Calcd (found)		
					C	H	N
5af	$C_{22}H_{20}ON_2$	7	85	175-	80.49	6.10	8.54
				176	(80.71)	(6.29)	(8.59)
5ag	$C_{26}H_{22}N_2$	1.4	98	167-	86.19	6.08	7.73
				168	(86.35)	(6.04)	(7.82)
5ah	$C_{21}H_{19}ON_3$	7	88	182-	76.60	5.77	12.76
				183	(76.74)	(5.84)	(12.72)
5bf	$C_{22}H_{19}ON_2Cl$	2.3	96	172-	72.83	5.24	7.72
				173	(72.70)	(5.29)	(7.54)
5bg	$C_{26}H_{21}N_2Cl$	1.7	98	131-	78.69	5.30	7.06
				132	(78.99)	(5.43)	(6.83)
5bh	$C_{21}H_{18}ON_3Cl$	6.4	82	162-	69.32	4.95	11.55
				164	(69.38)	(4.82)	(11.54)
5cf	$C_{21}H_{17}ON_2Cl$	1.5	99	177-	72.31	4.88	8.03
				178	(72.34)	(4.85)	(8.16)
5cg	$C_{25}H_{19}N_2Cl$	1.4	98	129-	78.43	4.97	7.32
				130	(78.58)	(5.12)	(7.52)
5ch	$C_{20}H_{16}ON_3Cl$	11	85	180-	68.67	4.58	12.02
				182	(68.87)	(4.67)	(11.88)
5df	$C_{22}H_{20}O_2N_2$	1.3	98	186-	76.74	5.81	8.14
				187	(76.93)	(5.59)	(8.54)
5dg	$C_{26}H_{22}ON_2$	1.2	98	135-	82.54	5.82	7.41
				136	(82.51)	(5.72)	(7.48)
5dh	$C_{21}H_{19}O_2N_3$	7.5	86	173-	73.04	5.51	12.17
				175	(73.12)	(5.46)	(12.21)
5ef	$C_{23}H_{23}ON_3$	4.5	85	183-	77.31	6.44	11.76
				184	(77.42)	(6.48)	(11.79)
5eg	$C_{27}H_{25}N_3$	2.2	99	185-	82.86	6.39	10.74
				186	(82.83)	(6.41)	(10.78)
5eh	$C_{22}H_{22}ON_4$	6.8	86	192-	73.74	6.14	15.64
				193	(73.87)	(6.34)	(15.28)

^a Yields of isolated products, calculated on the basis of the chalcones **3a-e**.

Table 2. IR, ^1H -NMR and MS (EI) spectral data of the 2-pyrazoline products

Compound	IR (cm^{-1})	^1H -NMR (ppm)	MS (m/z)
5af	3068, 2975, 1660, 1620, 1580, 1484, 1337, 1638, 806	2.38 (s, 3H, Me), 2.46 (s, 3H, COMe), 3.16 (dd, $J = 18.2, 5.1$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.80 (dd, $J = 18.2, 11.8$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.91 (dd, $J = 11.8, 5.1$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.12 (s, 4H, Ph), 7.25–8.00 (m, 7H, Naph)	57, 71, 77, 91, 127, 153, 255, 285, 286, 328, 329
5ag	3178, 2938, 2813, 1600, 1500, 1100, 870, 820, 750	2.40 (s, 3H, Me), 3.05 (dd, $J = 16.9, 8.4$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.82 (dd, $J = 16.9, 12.0$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.29 (dd, $J = 12.0, 8.4$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 6.60–8.20 (m, 16H, Ar)	42, 77, 91, 101, 118, 125, 127, 153, 167, 244, 271, 362
5ah	3500, 3350, 3115, 2985, 1675, 1580, 1500, 1160, 855, 760	2.23 (s, 3H, Me), 3.26 (dd, $J = 18.3, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.77 (dd, $J = 18.3, 12.4$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.33 (bs, 2H, NH_2), 5.50 (dd, $J = 12.4, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.08 (s, 4H, Ph), 7.20–8.00 (m, 7H, Naph)	42, 77, 91, 101, 127, 169, 153, 118, 195, 238, 285, 313, 329
5bf	3065, 2915, 1670, 1590, 1470, 1450, 1330, 1150, 975, 865, 745, 630	2.42 (s, 3H, Me), 2.52 (s, 3H, COMe), 3.16 (dd, $J = 18.0, 5.2$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.83 (dd, $J = 18.0, 12.0$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.92 (dd, $J = 12.0, 5.20$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.10–8.10 (m, 10H, Ar)	57, 71, 77, 112, 127, 138, 154, 271, 237, 277, 279, 294, 292, 305, 307, 308, 348, 350
5bg	3058, 2883, 1594, 1500, 1460, 1325, 1120, 1050, 865, 745, 700	2.38 (s, 3H, Me), 3.14 (dd, $J = 16.6, 8.1$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 4.11 (dd, $J = 16.6, 11.6$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.58 (dd, $J = 11.6, 8.1$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 6.50–8.20 (m, 15H, Ar)	77, 91, 101, 113, 111, 127, 138, 140, 153, 167, 244, 271, 382, 384
5bh	3450, 3250, 3085, 2965, 1680, 1580, 1478, 1240, 1075, 820, 750	2.28 (s, 3H, Me), 3.33 (dd, $J = 16.6, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.89 (dd, $J = 16.6, 12.2$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.38 (bs, 2H, NH_2), 5.60 (dd, $J = 12.2, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.26 (s, 3H, Ph), 7.38–8.20 (m, 7H, Naph)	42, 91, 115, 127, 153, 169, 196, 195, 249, 305, 307, 349, 351
5cf	3048, 2980, 1665, 1600, 1500, 1475, 1452, 1195, 986, 735, 640	2.42 (s, 3H, COMe), 3.12 (dd, $J = 18.0, 6.20$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.78 (dd, $J = 18.0, 12.6$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.95 (dd, $J = 18.0, 6.2$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.20 (s, 4H, Ph), 7.32–8.30 (m, 7H, Naph)	57, 77, 114, 127, 138, 153, 271, 237, 277, 276, 294, 292, 306, 307, 308, 348, 349, 350
5cg	3072, 2918, 1600, 1500, 1360, 1135, 825, 730	3.18 (dd, $J = 16.6, 8.5$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.83 (dd, $J = 16.6, 11.4$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.18 (dd, $J = 11.4, 8.5$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 6.60–8.20 (m, 16H, Ar)	77, 91, 101, 113, 127, 139, 140, 153, 168, 244, 271, 382, 383, 384
5ch	3420, 3300, 3120, 2900, 1675, 1582, 1487, 1500, 1220, 1085, 820, 745	3.25 (dd, $J = 17.4, 6.4$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.81 (dd, $J = 17.4, 12.2$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.35 (bs, 2H, NH_2), 5.48 (dd, $J = 12.2, 6.4$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 7.18 (s, 4H, Ph), 7.30–8.10 (m, 7H, Naph)	42, 77, 101, 115, 127, 153, 169, 196, 195, 228, 293, 305, 307, 349, 351
5df	3068, 2887, 2838, 1670, 1600, 1495, 1448, 1120, 1095, 954, 740	2.45 (s, 3H, COMe), 3.25 (dd, $J = 18.1, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 3.75 (s, 3H, OMe), 3.82 (dd, $J = 18.1, 12.2$ Hz, 1H, $\text{CH}(\text{Pyraz})$), 5.54 (dd, $J = 12.2, 5.8$ Hz, 1H, $\text{CH}_2(\text{Pyraz})$), 6.82 (d, $J = 9.5$ Hz, 2H, 3- H_{Ph}), 7.20 (d, $J = 9.5$ Hz, 2H, 2- H_{Ph}), 7.50–8.10 (m, 7H, Naph)	57, 77, 101, 108, 127, 134, 153, 167, 274, 301, 329, 344, 345

Table 2. Cont.

Compounds	IR (cm ⁻¹)	¹ H-NMR (ppm)	MS (m/z)
5dg	3150, 2880, 1600, 1495, 1410, 1350, 1240, 1115, 1035, 820, 740	3.29 (dd, <i>J</i> = 17.8, 6.0 Hz, 1H, CH ₂ (Pyraz)), 3.82 (dd, <i>J</i> = 17.8, 12.0 Hz, 1H, CH ₂ Pyraz), 3.70 (s, 3H, Me), 5.18 (dd, <i>J</i> = 12.0, 6.0 Hz, 1H, CH ₂ (Pyraz)), 6.60 - 8.20 (m, 16H, Ar)	77, 107, 127, 134, 153, 154, 167, 244, 271, 378
5dh	3480, 3375, 3150, 2900, 1685, 1580, 1520, 1490, 1250, 1070, 865, 750	3.27 (dd, <i>J</i> = 18.1, 5.0 Hz, 1H, CH ₂ (Pyraz)), 3.69 (s, 3H, Me), 3.78 (dd, <i>J</i> = 18.1, 11.2 Hz, 1H, CH ₂ Pyraz), 5.40 (bs, 2H, NH ₂), 5.52 (dd, <i>J</i> = 11.2, 5.0 Hz, 1H, CH ₂ (Pyraz)), 6.77 (d, <i>J</i> = 9.8 Hz, 2H, 3-H _{Ph}), 7.15 (d, <i>J</i> = 9.8 Hz, 2H, 2-H _{Ph}), 7.30 - 8.00 (m, 7H, Naph)	77, 91, 121, 134, 149, 153, 169, 191, 195, 303, 302, 345, 346
5ef	3087, 2983, 2810, 1657, 1648, 1615, 1595, 1340, 1075, 815	2.43 (s, 3H, COMe), 2.83 (s, 6H, NMe ₂), 3.12 (dd, <i>J</i> = 15.9, 7.9 Hz, 1H, CH ₂ (Pyraz)), 3.75 (dd, <i>J</i> = 15.9, 11.8 Hz, 1H, CH ₂ Pyraz), 5.85 (dd, <i>J</i> = 11.8, 7.9 Hz, 1H, CH ₂ (Pyraz)), 7.35 (d, <i>J</i> = 9.6 Hz, 2H, 3-H _{Ph}), 7.63 (d, <i>J</i> = 9.6 Hz, 2H, 2-H _{Ph}), 7.80 - 8.10 (m, 7H, Naph)	44, 77, 101, 110, 127, 137, 153, 167, 195, 237, 313, 314, 342, 357
5eg	3134, 3006, 2871, 1616, 1594, 1523, 1453, 1117, 865, 826, 747	2.79 (s, 6H, NMe ₂), 3.15 (dd, <i>J</i> = 15.5, 8.1 Hz, 1H, CH ₂ (Pyraz)), 3.71 (dd, <i>J</i> = 15.5, 11.2 Hz, 1H, CH ₂ Pyraz), 5.09 (dd, <i>J</i> = 11.2, 8.1 Hz, 1H, CH ₂ (Pyraz)), 6.30 - 8.20 (m, 16H, Ar)	48, 64, 77, 91, 120, 121, 134, 147, 153, 171, 244, 271, 389, 391, 392, 393
5eh	3120, 2818, 1660, 1635, 1600, 1589, 1348, 1150, 845, 650	2.81 (s, 6H, NMe ₂), 3.26 (dd, <i>J</i> = 15.0, 8.2 Hz, 1H, CH ₂ (Pyraz)), 3.82 (dd, <i>J</i> = 15.0, 12.2 Hz, 1H, CH ₂ Pyraz), 5.36 (bs, 2H, NH ₂), 5.68 (dd, <i>J</i> = 12.2, 8.2 Hz, 1H, CH ₂ (Pyraz)), 7.21 (d, <i>J</i> = 10.3 Hz, 2H, 3-H _{Ph}), 7.58 (d, <i>J</i> = 10.3 Hz, 2H, 2-H _{Ph}), 7.70 - 8.10 (m, 7H, Naph)	42, 77, 120, 127, 147, 153, 154, 169, 191, 195, 314, 358

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