Silica-Supported Synthesis of some 1,3,5-Trisubstituted 2-Pyrazolines under Solvent-free and Microwave Irradiation Conditions

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A simple method for the synthesis of 2-pyrazolines is described which occurs on silica surface under solvent-free conditions within 110-180 sec using microwave irradiation. The results obtained indicate that the use of silica gel as a support in pyrazoline formation reactions can have a profound effect on reaction rates and yields and cause cleaner reaction conditions.

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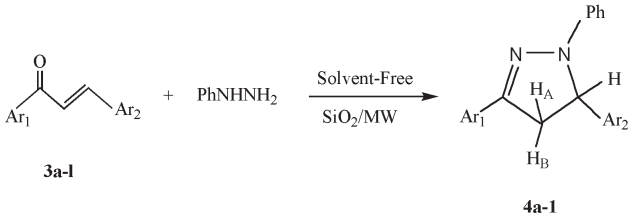
Variously substituted pyrazolines and their derivatives are important constituents that often exist in biologically active natural products [1]. They also serve as synthetic compounds of medicinal importance as analgesic, anti-inflammatory, antipyretic, anti-arrhythmic, tranquilizing, muscle relaxant, psycho analeptic agents [2]. Among them, 1,3,5-trisubstituted 2-pyrazolines can be conveniently prepared from chalcone derivatives and hydrazines *via* hydrazone intermediates which undergo an easy cyclization to afford 2-pyrazolines [3,4]. Pyrazolines have played a crucial part in five-membered heterocyclic chemistry and also utilized as valuable synthetic precursors in organic synthesis [5].

As it is evident from the literature [6], in recent years a significant portion of research in heterocyclic chemistry has been devoted to aryl-substituted pyrazolines. We have recently reported on the synthesis of some newly 3,5-dinaphthylated 2-pyrazolines, which efficiently acted against a variety of test organisms [7]. The increasingly reported ability of different supporting agents in improving the selectivity and reactivity of organic reactions [8] has prompted us to examine the pyrazoline formation under supporting conditions. Regarding that only polar reagents activated on the surfaces of various minerals can absorb microwave energy, a variety of reagents supported on such surfaces have been used to enhance the organic reactions using a simple microwave (MW) oven. On the other hand, solvent-free reactions seem to be highly useful and environmentally friendly technique in organic synthesis, especially when inorganic solid supports are used [9].

Here, we report an extremely facile and environmentally friendly method for the preparation of 1,3,5-trisubstituted 2-pyrazolines. We first prepared the intermediate chalcones 3a-l from aldol condensation reactions between ketones and aldehydes according to the literature [7]. These chalcones subsequently undergo a rapid cyclization with phenyl hydrazine under solvent-free and silica-supported conditions using microwave irradiation to afford 1,3,5-trisubstituted 2-pyrazolines 4a-l quantitatively in 110-180 sec (Scheme1).

The results obtained (Tables 1 and 2) indicate that the use of silica gel support can increase both the reaction rates and yields and cause cleaner reaction conditions.

Scheme 1



3a-l **4a-1**

Table 1

Substrates used in Silica-supported Synthesis of 1,3,5-Substituted 2-Pyrazolines

Substrate	Product	Ar_1	Ar_2
3a	**4a**	2-Naphthyl	2-MeC_6H_4
3b	**4b**	Ph	Ph
3c	**4c**	4-MeC_6H_4	3-MeC_6H_4
3d	**4d**	4-$MeOC_6H_4$	3-MeC_6H_4
3e	**4e**	4-$MeOC_6H_4$	2-MeC_6H_4
3f	**4f**	4-$MeOC_6H_4$	Ph
3g	**4g**	4-$MeOC_6H_4$	4-ClC_6H_4
3h	**4h**	3-MeC_6H_4	4-ClC_6H_4
3i	**4i**	2-Naphthyl	3-MeC_6H_4
3j	**4j**	2-Naphthyl	4-ClC_6H_4
3k	**4k**	2-Naphthyl	2-ClC_6H_4
3l	**4l**	4-$MeOC_6H_4$	2-ClC_6H_4

EXPERIMENTAL

All melting points were determined on a Büchi 530 melting point apparatus, and reported uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded for deuteriochloroform solution using tetramethylsilane as the internal standard on a Jeol FX (at 90 MHz) spectrometer at ambient temperature. ir spectra were recorded on a Shimadzu 435u-04 instrument using KBr pellets. Mass spectra were recorded on a GCMS-QP1100EX at Shahid Beheshti university, Tehran, Iran. The CHN analysis were carried out in Iranian Petroleum Research Center (Ray city, Tehran).

Table 2

1,3,5-Trisubstituted 2-Pyrazolines Produced Under Solvent-free (**I**) and Solvent-free/Silica-supported Conditions (**II**) using Microwave Irradiation

Substrate	Product [a]	IrradiationTime (sec)		Yield [b] (%)	MP (°C)
		I	II	I (II)	
3a	**4a**	150	120	49(60)	169-171
3b	**4b**	140	130	58(80)	129-131
3c	**4c**	200	150	38(74)	124-126
3d	**4d**	240	170	48(60)	112-114
3e	**4e**	240	170	46(64)	88-90
3f	**4f**	190	160	40(85)	134-136
3g	**4g**	210	180	38(62)	110-112
3h	**4h**	180	140	40(54)	105-107
3i	**4i**	200	160	40(69)	152-154
3j	**4j**	190	150	58(78)	160-162
3k	**4k**	160	110	40(74)	124-126
3l	**4l**	190	150	40(64)	148-150

[a] Products **4b, 4f, 4g** and **4j** are known which were characterized by ir, ^{1}H-nmr, ^{13}C-nmr and by direct comparison with literature values. [b] Isolated Yields calculated on the basis of the chalcones **3a-l**.

General procedure for Microwave-assisted Preparation of 1,3,5-Trisubstituted 2-Pyrazoline Derivatives **4a-l**.

A mixture of chalcone **3a-l** (2 mmol) and phenyl hydrazine reagent (2.4 mmol) was thoroughly mixed with 70-230 mesh silica gel (1g). The resulting mixture was placed in an alumina bath inside a MW oven (900 watts) and irradiated for 110-180 sec in the solid state. After complete conversion of the substrate as indicated by TLC, the product was extracted with Et_2O and the extract was filtered to remove the solid materials. The filtrate was then evaporated to leave a solid residue which was recrystallized from ethanol and the crystals were chromatographed on silica gel using acetone/petroleum ether (1:5) to obtain highly pure products **4a-l** as indicated below.

5-(*o*-Methylphenyl)-3-(2-naphthyl)-1-phenyl-2-pyrazoline (**4a**).

Compound **4a** was obtained in 60% yield; mp 169-171° (recrystallization from ethanol); ir (KBr): 3021, 2879, 1596, 1499, 1140, 740 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.39 (s, 3H, Me), 3.05 (dd, 1H, CHH_A), 3.81 (dd, 1H, CH_BH), 5.3 (dd, 1H, $CHAr_2$), 6.69-8.01 (m, 16H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 19.47(Me), 41.74 (CH_2), 61.68 ($CHAr_2$), 146.67 (C=N), 144.68, 140.08, 133.83, 133.36, 130.94 (C, arom), 129.01, 128.18, 127.38, 126.91, 126.37, 125.62, 124.98, 123.561, 119.19, 113.26 (CH, arom). ms: m/z 42, 77, 91, 101, 118, 125, 127, 153, 167, 244, 271, 362.

Anal. Calcd. for $C_{26}H_{22}N_2$: C, 86.19; H, 6.08; N, 7.73. Found: C, 86.0; H, 6.10; N, 7.76.

1,3,5-Triphenyl-2-pyrazoline (**4b**).

Compound **4b** was obtained in 80% yield; mp 129-131° (recrystallization from ethanol) (Lit. [10] mp 130-132°).

5-(*m*-Methylphenyl)-3-(*p*-methylphenyl)-1-phenyl-2-pyrazoline (**4c**).

Compound **4c** was obtained in 74% yield; mp 124-126° (recrystallization from ethanol); ir (KBr): 3030, 2917, 1597, 1499, 1131, 743 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.33 (s, 6H, 2Me), 3.12 (dd, 1H, CHH_A), 3.70 (dd, 1H, CH_BH), 5.19 (dd, 1H, $CHAr_2$), 7.12-7.57 (m, 13H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 21.42 (2Me), 42.14 (CH_2), 64.30 ($CHAr_2$), 149.68 (C=N), 142.5, 138.92, 137.71, 133.21, 131.92 (C, arom), 130.12, 129.12, 128.64, 127.10, 124.98, 123.12, 121.12, 114.04, 113.33 (CH, arom).

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.66; H, 6.75; N, 8.59. Found: C, 84.92; H, 6.78; N, 8.62.

5-(*m*-Methylphenyl)-3-(*p*-methoxyphenyl)-1-phenyl-2-pyrazoline (**4d**).

Compound **4d** was obtained in 60% yield; mp 112-114° (recrystallization from ethanol); ir (KBr): 3022, 2838, 1597, 1498, 1114, 748 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.17 (s, 3H, Me), 2.97 (dd, 1H, CHH_A), 3.66 (m, 4H, CH_BH, OMe), 4.96 (dd, 1H, $CHAr_2$), 6.71-7.47 (m, 13H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 21.09 (Me), 43.85 (CH_2), 55.29 (OMe), 64.30 ($CHAr_2$), 146.87 (C=N), 160.14, 145.30, 139.87, 137.12, 133.44 (C, arom), 130.12, 129.67, 128.87, 127.24, 125.86, 125.64, 128.78, 114.04, 113.33 (CH, arom).

Anal. Calcd. for $C_{23}H_{22}ON_2$: C, 80.70; H, 6.43; N, 8.19. Found: C, 80.45; H, 6.46; N, 8.22.

5-(*o*-Methylphenyl)-3-(*p*-methoxyphenyl)-1-phenyl-2-pyrazoline (**4e**).

Compound **4e** was obtained in 64% yield; mp 88-90° (recrystallization from ethanol); ir (KBr): 3041, 2933, 1652, 1597, 1182, 761 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.37 (s, 3H, Me), 2.91 (dd, 1H, CHH_A), 3.72 (m, 4H, CH_BH, OMe), 5.21 (dd, 1H, $CHAr_2$), 6.85-7.91 (m, 13H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 21.98 (Me), 44.35 (CH_2), 56.48 (OMe), 64.90 ($CHAr_2$), 148.82 (C=N), 159.94, 144.42, 140.14, 136.14, 132.68 (C, arom), 130.42, 129.24, 128.76, 126.32, 124.98, 123.68, 121.62, 114.04, 112.48 (CH, arom).

Anal. Calcd. for $C_{23}H_{22}ON_2$: C, 80.70; H, 6.43; N, 8.19. Found: C, 80.58; H, 6.40; N, 8.23.

3-(p-Methoxyphenyl)-1,5-(diphenyl)-2-pyrazoline (**4f**).

Compound **4f** was obtained in 85% yield; mp 134-136° (recrystallization from ethanol) (Lit. [11] mp 135-137°).

5-(*p*-Chlorophenyl)-3-(*p*-methoxyphenyl)-1-phenyl-2-pyrazoline (**4g**).

Compound **4g** was obtained in 62% yield; mp 110-112° (recrystallization from ethanol) (Lit. [11] mp 115-117°).

5-(p-Chlorophenyl)-3-(m-Methylphenyl)-1-phenyl-2-pyrazoline (**4h**).

Compound **4h** was obtained in 54% yield; mp 105-107° (recrystallization from ethanol); ir (KBr): 3032, 2918, 1633, 1597, 1116, 822 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.42 (s, 3H, Me), 2.75 (dd, 1H, CHH_A), 3.12 (dd, 1H, CH_BH), 5.17 (dd, 1H, $CHAr_2$), 6.69-7.46 (m, 13H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 21.44 (Me), 42.387 (CH_2), 62.12 ($CHAr_2$), 150.62 (C=N), 142.5, 138.92, 137.71, 133.21, 131.92 (C, arom), 130.57, 129.95, 129.21, 128.05, 127.69, 126.23, 124.56, 113.12, 112.10 (CH, arom).

Anal. Calcd. for $C_{22}H_{19}N_2Cl$: C, 76.19; H, 5.48; N, 8.08. Found: C, 76.53; H, 5.50; N, 8.12.

5-(*m*-Methylphenyl)-3-(2-naphthyl)-1-phenyl-2-pyrazoline (**4i**).

Compound **4i** was obtained in 69% yield; mp 152-154° (recrystallization from ethanol); ir (KBr): 2925, 2856, 1598, 1495, 1104, 754 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 2.38 (s, 3H, Me), 3.33 (dd, 1H, CHH_A), 3.92 (dd, 1H, CH_BH), 5.27 (dd, 1H, $CHAr_2$), 6.87-8.20 (m, 16H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 21.47 (Me), 43.59 (CH_2), 64.80 ($CHAr_2$), 147.14 (C=N), 145.07, 142.80, 138.93, 133.47, 130.59 (C, arom), 128.98, 128.42, 128.18, 127.86, 126.46, 125.09, 123.62, 123.04, 119.28, 113.66 (CH, arom).

Anal. Calcd. for $C_{26}H_{22}N_2$: C, 86.19; H, 6.08; N, 7.73. Found: C, 85.92; H, 6.05; N, 7.75.

5-(*p*-Chlorophenyl)-3-(2-naphthyl)-1-phenyl-2-pyrazoline (**4j**).

Compound **4j** was obtained in 78% yield; mp 160-162° (recrystallization from ethanol) (Lit.[11] 156-158°).

5-(o-Chlorophenyl)-3-(2-naphthyl)-1-phenyl-2-pyrazoline (**4k**).

Compound **4k** was obtained in 74% yield; mp 124-126° (recrystallization from ethanol); ir (KBr): 3054, 1598, 1496, 1146, 750 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 3.14 (dd, 1H, CHH_A), 4.11 (dd, 1H, CH_BH), 5.58 (dd, 1H, $CHAr_2$), 6.73-8.03 (m, 16H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 42.11 (CH_2), 63.24 ($CHAr_2$), 149.46 (C=N), 144.24, 138.90, 137.98, 135.11, 133.12, 131.09 (C, arom), 130.00, 129.26, 128.84, 127.14, 125.84, 125.18, 123.12, 121.01, 118.24, 113.16, 112.04 (CH, arom).

Anal. Calcd. for $C_{25}H_{19}N_2Cl$: C, 78.43; H, 4.97; N, 7.32. Found: C, 78.72; H, 4.95; N, 7.36.

5-(*o*-Chlorophenyl)-3-(*p*-methoxyphenyl)-1-phenyl-2-pyrazoline (**4l**).

Compound **4l** was obtained in 64% yield; mp 148-150° (recrystallization from ethanol); ir (KBr): 2933, 2835, 1597, 1497, 1122, 747 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ= 3.11 (dd, 1H, CHH_A), 3.85 (m, 3H, OMe), 5.16 (s, 1H, CH_BH), 5.62 (dd, 1H, $CHAr_2$), 6.91-7.67 (m, 13H, Ar). ^{13}C-nmr ($CDCl_3$): δ= 77.10 ($CDCl_3$), 41.38 (CH_2), 54.98 (OMe), 63.44 ($CHAr_2$), 146.87 (C=N), 159.90, 144.69, 142.06, 140.93, 135.76 (C, arom), 130.50, 129.20, 127.04, 126.92, 124.92, 121.96, 120.53, 118.73, 113.71 (CH, arom).

Anal. Calcd. for $C_{22}H_{19}ON_2Cl$: C, 72.83; H, 5.24; N, 7.72. Found: C, 72.52; H, 5.27; N, 7.69.

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