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A MODIFIED AND CONVENIENT METHOD FOR THE PREPARATION OF N-PHENYLPYRAZOLINE DERIVATIVES

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Ten new N-phenylpyrazoline derivatives have been synthesized in high yields by condensation of chalcones with phenylhydrazine in the presence of potassium carbonate in reflux conditions. The work-up is simple and involves treatment with ice-cold water. As compared with the previous method a considerable increase in the reaction rate with better yields has been observed.

Keywords: chalcones, N-phenylpyrazolines, intramolecular cyclization, Michael addition.

N-Phenylpyrazoline derivatives are important compounds in organic chemistry because of their application in heterocyclic synthesis and medicine [1]. Pyrazolines have been reported to show a wide spectrum of biological activity, including antibacterial [2], antifungal [3], anti-inflammatory [4], antiamoebic [5], and antidepressant activity [6]. The pyrazoline function is quite stable, and has inspired chemists to utilize the mentioned stable fragment in bioactive moieties to synthesize new compounds possessing biological activity. Some related compounds were evaluated for anticon- vulsant activity [7]. The antidepressant activity of these compounds was evaluated by the "Porsolt Behavioural Despair Test" on Swiss–Webster mice [8].

The α,β-unsaturated ketones can play the role of versatile precursors in the syntheses of the corresponding pyrazoline derivatives [9-14]. The reaction of hydrazine and its derivatives with α,β-unsaturated ketones and α,β-epoxy ketones is one of the preparative methods for the synthesis of pyrazolines and pyrazoles [15]. Alternatively, the reaction of substituted hydrazines with α,β-unsaturated ketones has been reported to lead to regioselective formation of pyrazolines [16, 17].

The synthesis of pyrazoline rings from chalcone derivatives containing anisole and the 3,4-methylenedioxyphenyl ring by the conventional method using acetic acid was reported with low yields [18]. We have developed a general and efficient method for the synthesis of N-phenylpyrazoline derivatives from chalcones and phenylhydrazine under reflux conditions in the presence of potassium carbonate as a catalyst (Scheme 1).

Chalcones **3a-j** were synthesized by aldol condensation reaction of acetophenone derivatives **1** and aromatic aldehydes **2** in the presence of basic catalysts [19]. Pyrazoline derivatives were synthesized by using 1 mol of chalcones **3a-j** and 1.3 mol of phenylhydrazine in the presence of potasium carbonate under reflux conditions. Compounds **4a-j** were prepared in an oil bath (120°C) using potasium carbonate in accordance with conventional methods. The hydrazination reaction involves initial nucleophilic attack in the β-position of the chalcone nucleus and ring closure with nucleophilic attack on the carbonyl group of chalcone.

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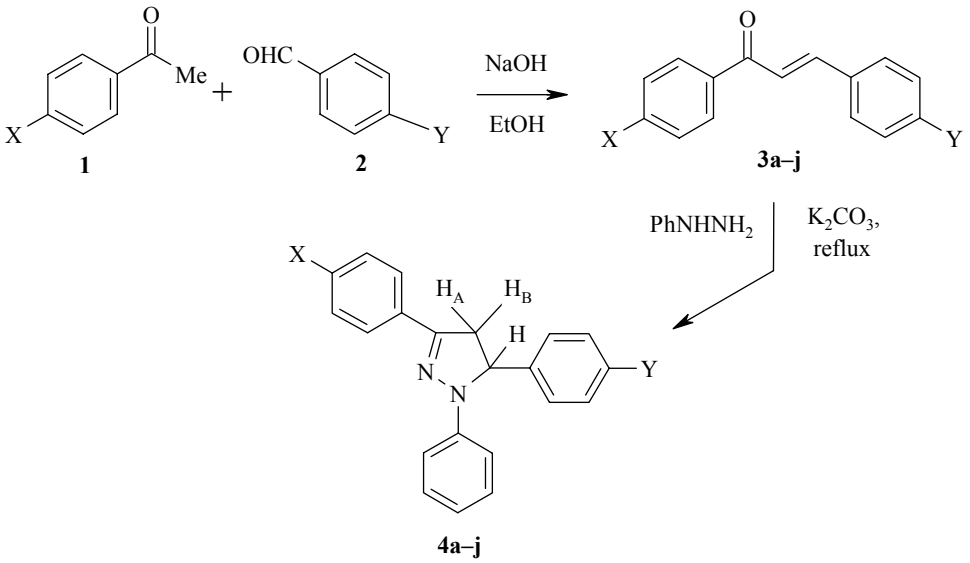
Scheme 1



The synthesis of compounds **4a-j** using K_2CO_3 in reflux conditions (Method B) was attempted under identical conditions using acetic acid (Method A) [18]. Lower yields were obtained in method A as compared with B. An increase in the polarity of molecules in the presence of the basic catalyst (K_2CO_3) in polar protic solvents led to a greater reactivity of the nucleophile in the Michael addition reaction and intramolecular cyclizations. Meanwhile, this is consistent with the reaction mechanism, which involves a polar transition state [20] stabilized by polar protic solvents. Finally, nucleophilic attack on the carbonyl group by intramolecular cyclization resulted in the formation of pyrazoline derivatives. The reaction was clean with good to excellent yields (Table 1) except **4i** which has a low yield of 45%.

In this article, we present an easy and effective method for the preparation of new pyrazoline derivatives in high yield under reflux conditions using K_2CO_3. This method may be used to prepare heterocyclic compounds, which have a wide application in organic synthesis.

TABLE 1. Reaction of Chalcones with Phenylhydrazine in Reflux Conditions

Entry	Product	X	Y	Time, min	Yield, %*	Time, min	Yield, %*
				Method A		Method B	
1	**4a**	H	H	110	65	80	80
2	**4b**	Cl	H	45	65	14	85
3	**4c**	H	Cl	40	58	12	80
4	**4d**	Cl	Cl	30	87	5	95
5	**4e**	H	Br	45	70	15	90
6	**4f**	Cl	Br	38	78	10	93
7	**4g**	H	Me	140	43	100	64
8	**4h**	Cl	Me	87	53	60	76
9	**4i**	H	NMe_2	155	28	120	45
10	**4j**	Cl	NMe_2	105	53	70	70

* Yield of isolated products.

EXPERIMENTAL

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. The progress of the reactions was monitored by TLC on Riedel-de Haën plates coated with silica gel 60 F_{254} in a 75:25 petroleum ether–ethyl acetate system. IR spectra were taken in thin layer on Magna-Nicolet IR 550 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance DRX-400 spectrometer in $CDCl_3$ with TMS as an internal reference. Mass-spectra were recorded on a Finnigan MAT 44S, with an ionization voltage of 70 eV. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer.

Synthesis of New N-Phenylpyrazoline Derivatives (General Procedure). A. Phenylhydrazine (13 mmol) was added to a chalcone (10 mmol) in acetic acid (15 ml). The mixture was refluxed under constant stirring for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with ice-cold water .The solid was collected, washed with water and recrystallized from ethanol as pale yellow plates.

B. Potassium carbonate (10 mol% w/w of chalcone) was added to a solution of phenylhydrazine (13 mmol) and chalcone (10 mmol) in ethanol (15 ml). The mixture was refluxed under constant stirring for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the workup was the same as in method A.

1,3,5-Triphenyl-2-pyrazoline (4a). Yield 2.3 g, 80%, yellow prisms; mp 139-141°C. IR spectrum, ν, cm^{-1}: 3027, 1588, 1490. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.22 (1H, dd, J_1 = 17.1, J_2 = 7.2, C$\underline{H}_A$H$_B$C=N); 3.87 (1H, dd, J_1 = 17.1, J_2 = 12.2, CH$_A\underline{H}_B$C=N); 5.34 (1H, dd, J_1 = 12.2, J_2 = 7.2, ArCHN); 6.97-7.89 (m, 15 aromatic H). ^{13}C NMR spectrum, δ, ppm: 43.7 (CH_2); 64.90 (Ar$\underline{C}$HN); 113.8, 119.3, 125.8, 126.0, 127.50, 128.50, 129.1, 133.1, 142.8, 143.9, 145.3, 146.8 (aromatic C), 150.2 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 298 [M]$^+$ (83), 91 (100). Found, %: C 84.45; H 6.10; N 4.71. $C_{21}H_{18}N_4$. Calculated, %: C 84.53; H 6.08; N 4.69.

3-(4-Chlorophenyl)-1,5-diphenyl-2-pyrazoline (4b). Yield 2.8 g, 85%, yellow powder; mp 149-151°C. IR spectrum, ν, cm^{-1}: 3028, 1593, 1490. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.15 (1H, dd, J_1 = 17.2, J_2 = 7.2, C$\underline{H}_A$H$_B$C=N); 3.80 (1H, dd, J_1 = 17.2, J_2 = 12.4, CH$_A\underline{H}_B$C=N); 5.29 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC$\underline{H}$N); 6.68-7.70 (m, 14 aromatic H). ^{13}C NMR spectrum, δ, ppm: 43.5 (CH_2); 65.1 (ArCHN); 113.8, 119.6, 125.9, 126.9, 127.6, 128.8, 129.1, 131.6, 134.4, 142.5, 145.0, 145.5 (aromatic C), 151.2 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 332 [M]$^+$ (86), 334 [M+2]$^+$ (28), 91 (100). Found, %: C 75.80; H 5.13; N 8.40. $C_{21}H_{17}ClN_2$. Calculated, %: C 75.78; H 5.14; N 8.41.

5-(4-Chlorophenyl)-1,3-diphenyl-2-pyrazoline (4c). Yield 2.6 g, 80%, yellow powder; mp 147-149°C. IR spectrum, ν, cm^{-1}: 3057, 1588, 1495. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.13 (1H, dd, J_1 = 17.2, J_2 = 7.2, C$\underline{H}_A$H$_B$C=N); 3.83 (1H, dd, J_1= 17.2, J_2 = 12.4, CH$_A\underline{H}_B$C=N); 5.25 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC$\underline{H}$N); 6.91-7.82 (m, 14 aromatic H). ^{13}C NMR spectrum, δ, ppm: 43.59 (CH_2); 65.1 (Ar$\underline{C}$HN); 113.85, 119.62, 125.86, 127.45, 128.93, 129.33, 130.04, 132.88, 133.51, 141.30, 145.09, 146.85 (aromatic C), 149.1 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 332 [M]$^+$ (83), 334 [M+2]$^+$ (27), 91 (100). Found, %: C 75.76; H 5.13; N 8.40. $C_{21}H_{17}ClN_2$. Calculated, %: C 75.78; H 5.15; N 8.41.

3,5-Bis(4-chlorophenyl)-1-phenyl-2-pyrazoline (4d). Yield 3.4 g, 95%, yellow powder; mp 167-169°C. IR spectrum, ν, cm^{-1}: 3029, 1593, 1480. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08-3.12 (1H, dd, J_1 = 17.2, J_2 = 7.2, C$\underline{H}_A$H$_B$C=N); 3.82 (1H, dd, J_1 = 17.2, J_2 = 12.4, CH$_A\underline{H}_B$C=N); 5.28 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC$\underline{H}$N); 6.81-7.64 (m, 13 aromatic H). ^{13}C NMR spectrum, δ, ppm: 45.0 (CH_2), 66.0 (Ar$\underline{C}$HN), 106.7, 115.4, 121.4, 126.9, 128.7, 130.5, 131.5, 135.2, 136.2, 142.5, 145.1, 147.1 (aromatic C), 152.6 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 371 [M+4]$^+$ (14), 369 [M+2]$^+$ (60), 367 [M]$^+$ (80), 91 (100). Found, %: C 68.66; H 4.40; N 7.65. $C_{21}H_{16}Cl_2N_2$. Calculated, %: C 68.67; H 4.39; N 7.62.

5-(4-Bromophenyl)-1,3-diphenyl-2-pyrazoline (4e). Yield 3.3 g, 90%, yellow powder; mp 169-171°C. IR spectrum, ν, cm^{-1}: 3027, 1593, 1495. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (1H, dd, J_1 = 17.2, J_2 = 7.2, C$\underline{H}_A$H$_B$C=N); 3.84 (1H, dd, J_1 = 17.2, J_2 = 12.4, CH$_A\underline{H}_B$C=N); 5.23 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC$\underline{H}$N);

6.80-7.72 (m, 14 aromatic H). ^{13}C NMR spectrum, δ, ppm: 43.59 (CH_2), 65.1 (Ar<u>C</u>HN), 113.85, 119.62, 125.86, 127.45, 128.55, 128.93, 129.33, 130.04, 132.88, 133.51, 141.30, 145.09 (aromatic C), 150.0 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 379 $[M+2]^+$ (80), 377 $[M]^+$ (79), 91 (100). Found, %: C 66.87; H 4.54; N 7.43. $C_{21}H_{17}BrN_2$. Calculated, %: C 66.85; H 4.54; N 7.42.

5-(4-Bromophenyl)-3-(4-chlorophenyl)-1-phenyl-2-pyrazoline (4f). Yield 3.8 g, 93%, yellow powder; mp 174-176°C. IR spectrum, ν, cm^{-1}: 3029, 1594, 1495. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.29 (1H, dd, J_1 = 16.8, J_2 = 7.2, C<u>H</u>$_A$H$_B$C=N); 4.02 (1H, dd, J_1 = 16.8, J_2 = 12.4, CH$_A$<u>H</u>$_B$C=N); 5.47 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC<u>H</u>N); 7.04-7.87 (m, 13 aromatic H). ^{13}C NMR spectrum, δ, ppm: 43.3 (CH_2), 65.1 (Ar<u>C</u>HN), 113.67, 119.75, 125.29, 126.87, 127.63, 128.75, 128.90, 130.16, 131.21, 132.31, 134.55, 141.45 (aromatic C), 149.2 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 415 $[M+4]^+$ (25), 413 $[M+2]^+$ (97), 411 $[M]^+$ (82), 91 (100). Found, %: C 61.26; H 6.90; N 6.81. $C_{21}H_{16}N_2CLBr$. Calculated, %: C 61.26; H 3.91; N 6.80.

5-(4-Methylphenyl)-1,3-diphenyl-2-pyrazoline (4g). Yield 1.9 g, 64%, yellow powder; mp 157-159°C. IR spectrum, ν, cm^{-1}: 3027, 1598, 1495. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.91 (1H, dd, J_1 = 17.2, J_2 = 7.2, C<u>H</u>$_A$H$_B$C=N); 3.59 (1H, dd, J_1 = 17.2, J_2 = 12.2, CH$_A$<u>H</u>$_B$C=N); 5.07 (1H, dd, J_1 = 12.2, J_2 = 7.2, ArC<u>H</u>N); 6.63-7.47 (m, 14 aromatic H). ^{13}C NMR spectrum, δ, ppm: 21.09 (CH_3), 43.50 (CH_2), 65.1 (Ar<u>C</u>HN), 105.1, 113.9, 119.5, 125.9, 126.9, 127.4, 128.7, 129.1, 131.6, 134.4, 142.5, 145.0 (aromatic C), 148.2 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 312 $[M]^+$ (77), 91 (100). Found, %: C 84.56; H 6.45; N 8.96. $C_{22}H_{20}N_2$ Calculated, %: C 84.58; H 6.45; N 8.96.

3-(4-Chlorophenyl)-5-(4-methylphenyl)-1-phenyl-2-pyrazoline (4h). Yield 2.6 g, 76%, yellow powder; mp 162-164°C. IR spectrum, ν, cm^{-1}: 3037, 1593, 1490. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s); 3.11 (1H, dd, J_1 = 17.2, J_2 = 7.2, C<u>H</u>$_A$H$_B$C=N); 3.78 (1H, dd, J_1 = 17.2, J_2 = 12.4, CH$_A$<u>H</u>$_B$C=N); 5.25 (1H, dd, J_1 = 12.4, J_2 = 7.2, ArC<u>H</u>N); 6.66-7.69 (m, 16 aromatic). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_3) 43.50 (CH_2), 64.7 (Ar<u>C</u>HN), 113.70, 119.4, 125.8, 126.9, 128.7, 129.8, 131.6, 134.3, 137.3, 139.5, 144.9, 145.50 (aromatic C), 149.5 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 348 $[M+2]^+$ (26), 346 $[M]^+$ (78), 91 (100) Found, %: C 76.19; H 5.52; N 8.10. $C_{22}H_{19}ClN_2$. Calculated, %: C 76.18; H 5.52; N 8.07.

5-(4-Dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline (4i). Yield 1.5 g, 45%, yellow powder; mp 161-163°C. IR spectrum, ν, cm^{-1}: 3027, 1603, 1489. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.96 (6H, s, 2CH_3); 3.16 (1H, dd, J_1 = 17.1, J_2 = 7.2, C<u>H</u>$_A$H$_B$C=N); 3.81 (1H, dd, J_1 = 17.1, J_2 = 12.2, CH$_A$<u>H</u>$_B$C=N); 5.23 (1H, dd, J_1 = 12.2, J_2 = 7.2, ArC<u>H</u>N); 6.74-7.78 (m, 14 aromatic H). ^{13}C NMR spectrum, δ, ppm: 40.50 (CH_3) 43.7 (CH_2), 64.6 (Ar<u>C</u>HN), 113.4, 113.8, 119.0, 125.7, 126.8, 128.3, 128.4, 128.7, 131.0, 133.3, 145.4, 146.7 (aromatic C), 150.0 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 341 $[M]^+$ (81), 91 (100). Found, %: C 80.91; H 6.78; N 12.30. $C_{23}H_{23}N_3$. Calculated, %: C 80.90; H 6.78; N 12.30.

3-(4-Chlorophenyl)-5-(4-dimethylaminophenyl)-1-phenyl-2-pyrazoline (4j). Yield 2.6 g, 70%, yellow powder; mp 167-169°C. IR spectrum, ν, cm^{-1}: 3037, 1588, 1495. H NMR spectrum, δ, ppm (*J*, Hz): 2.95 (6H, s, 2CH_3); 3.11 (1H, dd, J_1 = 17.1, J_2 = 7.2, C<u>H</u>$_A$H$_B$C=N); 3.75 (1H, dd, J_1 = 17.1, J_2 = 12.4, CH$_A$<u>H</u>$_B$C=N); 5.23 (1H, dd, J_1 = 12.4, J_{2s} = 7.2, ArC<u>H</u>N); 6.73-7.68 (m, 13 aromatic H). ^{13}C NMR spectrum, δ, ppm: 40.50 (CH_3) 43.5(CH_2), 64.7(Ar<u>C</u>HN), 113.4, 113.9, 119.3, 126.8, 127.8, 128.6, 128.7, 130.7, 131.9, 134.2, 145.2, 145.5, (aromatic C) 150.1 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 377 $[M+2]^+$ (28), 375 $[M]^+$ (89), 91 (100). Found, %: C 73.49; H 5.87; N 11.16. $C_{23}H_{22}ClN_3$. Calculated, %: C 73.49; H 5.89; N 11.17.

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