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A MILD AND HIGHLY EFFICIENT ONE-POT SYNTHESIS OF 1,3,5-TRIARYL-2-PYRAZOLINES

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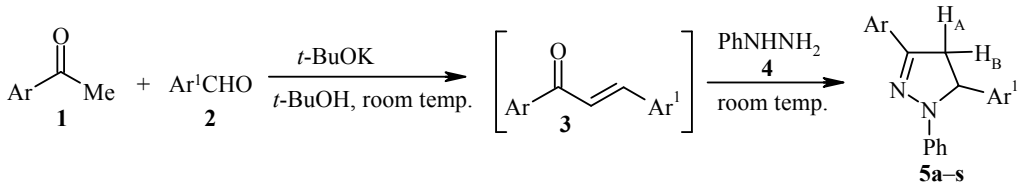
Pyrazolines are prominent 5-membered nitrogen-containing heterocyclic compounds, which play a crucial role in the development of heterocyclic chemistry theory and are also extensively used as valuable synthons in organic synthesis [1]. Among its various derivatives, 2-pyrazolines (4,5-dihydro-1*H*-pyrazines) seem to be the most frequently studied pyrazoline-type compounds. One of the most popular methods for the preparation of 2-pyrazolines involves the reaction of α,β-unsaturated aldehydes and ketones with hydrazines [2]. Because of various disadvantages, such as long reaction times, high temperatures, and two-step procedures encountered in the reported methodologies, we decided to develop a more efficient and convenient method. As far as we know, there is only one report on constructing 1,3,5-triaryl-2-pyrazolines by one-pot reaction of an aryl aldehyde, acetophenone derivatives, and phenylhydrazine in 10% NaOH [3], but the reaction mixture was refluxed in ethanol for relatively long times.

We have now developed an improved and highly convenient methodology for the synthesis of 3,5-diaryl-1-phenyl-2-pyrazoline derivatives *via* the reaction of phenylhydrazine with various chalcones, generated *in situ* by Claisen–Schmidt condensation of aryl methyl ketones and aldehydes, with catalytic amounts of *t*-BuOK (5 mol%) in anhydrous *t*-BuOH at room temperature.



To establish the generality of this process, various acetophenones and aromatic aldehydes possessing either electron-withdrawing or electron-donating groups were treated with phenylhydrazine (Table 1). These reactions were in general very fast (3–13 min) and clean, and 2-pyrazolines were obtained as the sole products in high yields (69-89%). Surprisingly, the reactions of acetophenone with 4-nitrobenzaldehyde and 9-anthraldehyde

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TABLE 1. *t*-BuOK-Catalysed One-pot Synthesis of 3,5-Diaryl-1-phenyl-2-pyrazolines

Compound	Ar	Ar[1]	Time, min	Yield*, %	Mp, °C
5a	Ph	Ph	6	87	135-137 (134-135 [4])
5b	Ph	4-$MeOC_6H_4$	5	81	121-123 (110-113 [4])
5c	Ph	2-ClC_6H_4	11	82	135-137 (134-135 [5])
5d	Ph	4-MeC_6H_4	5	79	133-135 (128-130 [4])
5e	Ph	4-ClC_6H_4	13	82	135-137 (135-136 [4])
5f	Ph	1-Naphthyl	11	69	174-176 (173-174 [6])
5g	Ph	4-$O_2NC_6H_4$	24 h	—	—
5h	Ph	9-Anthranyl	24 h	—	—
5i	Ph	4-NCC_6H_4	8	83	178-180 (151-152 [7])
5j	4-MeC_6H_4	4-MeC_6H_4	6	82	144-146 (143-145 [8])
5k	4-MeC_6H_4	4-ClC_6H_4	11	77	142-144 (155 [9])
5l	4-ClC_6H_4	Ph	6	87	148-149 (149-151 [10])
5m	4-ClC_6H_4	4-ClC_6H_4	6	73	154-156 (167-169 [10])
5n	4-ClC_6H_4	4-MeC_6H_4	3	88	151-153 (162-164 [10])
5o	4-ClC_6H_4	4-BrC_6H_4	5	86	173-175 (174-176 [10])
5p	4-$MeOC_6H_4$	4-$MeOC_6H_4$	11	78	145-147 (147-148 [6])
5q	4-BrC_6H_4	4-ClC_6H_4	9	84	152-154 (120 [9])
5r	4-BrC_6H_4	Ph	6	85	135-137 (144-147 [5])
5s	4-FC_6H_4	4-ClC_6H_4	3	89	146-148 (110 [9])

* Yields of pure isolated products.

did not produce the expected 2-pyrazolines (**5g**,**h**, Table 1) after prolonged reaction times (24 h) and even at reflux. It was observed that in the synthesis of compound **5g** the low solubility of the corresponding chalcone in *t*-BuOH prevented its reaction with phenylhydrazine, while in the case of compound **5h** the expected chalcone was not formed at all.

In conclusion, we have developed a new convenient and efficient method for the one-pot synthesis of 3,5-di-aryl-1-phenyl-2-pyrazolines. This method offers significant advantages over earlier reported procedures, in that it avoids the need to prepare and isolate chalcones and features a simple reaction procedure, mild conditions, very short reaction times, and high product yields.

IR spectra (KBr) were obtained using an ABB FTLA 2000 instrument. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AQS-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ solution using TMS as internal standard. Melting points were determined on a Büchi B-540 apparatus and were uncorrected. Chemicals were purchased from Merck.

Synthesis of Compounds 5a–s (General Method). A solution of *t*-BuOK (0.011 g, 0.1 mmol) in dry *t*-BuOH (2 ml) was placed in a round-bottom flask. With stirring at room temperature (25°C), a mixture of aldehyde (2.0 mmol) and ketone (2.0 mmol) was added to the above solution, and stirring was continued for several minutes. The progress of the reaction was monitored by TLC (*n*-hexane–EtOAc, 4:1) until the starting materials had completely disappeared; then phenylhydrazine (3.0 mmol) is added, and the mixture was stirred until completion of the reaction. The solid product was collected after filtration, washed with water, and recrystallized from 95% EtOH. Spectral data of compounds **5a**–**e**,**g**,**h**,**j**-**o**,**q**-**s** corresponded to that given in the literature.

5-(1-Naphthyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazine (5f). IR spectrum, ν, cm^{-1}: 1602 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (1H, dd, *J* = 16.9, *J* = 6.7, 4-C$\underline{H}_A$H$_B$); 4.07 (1H, dd, *J* = 16.9, *J* = 12.6, 4-CH$_A\underline{H}_B$); 5.96 (1H, dd, *J* = 12.6, *J* = 6.7, 5-CH); 6.82 (1H, t, *J* = 7.2, H Ar); 7.08-7.80 (14H, m, H Ar); 7.97 (1H, d, *J* = 7.8, H Ar); 8.12 (1H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 42.7 (C-4); 63.2 (C-5); 113.3,

119.1, 122.9, 123.3, 125.7, 125.8, 126.0, 126.5, 128.1, 128.6, 128.7, 129.0, 129.3, 129.9, 132.7, 134.4, 136.6, 147.3 (C Ar); 144.9 (C-3).

5-(4-Cyanophenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazine (5i). IR spectrum, ν, cm^{-1}: 1597 (C=N); 2228 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (1H, dd, *J* = 17.0, *J* = 7.0, 4-C$\underline{H}_A$H$_B$); 3.88 (1H, dd, *J* = 17.0, *J* = 12.7, 4-CH$_A\underline{H}_B$); 5.32 (1H, dd, *J* = 12.7, *J* = 7.0, 5-CH); 6.79-7.74 (14H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 43.3 (C-4); 64.0 (C-5); 111.6 (C≡N); 113.3, 118.6, 119.7, 125.8, 126.8, 128.7, 129.0, 129.1, 132.2, 133.1, 144.4, 147.8 (C Ar); 146.8 (C-3).

5,3-Bis(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazine (5p). IR spectrum, ν, cm^{-1}: 1597 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.09 (1H, dd, *J* = 17.0, *J* = 7.3, 4-C$\underline{H}_A$H$_B$); 3.73-3.85 (1H, m, 4-CH$_A\underline{H}_B$); 3.79 (3H, s, OCH$_3$); 3.85 (3H, s, OCH$_3$); 5.18 (1H, dd, *J* = 12.1, *J* = 7.3, 5-CH); 6.79 (1H, t, *J* = 7.2, H Ar); 6.88 (2H, d, *J* = 8.6, H Ar); 6.93 (2H, d, *J* = 8.8, H Ar); 7.08-7.28 (6H, m, H Ar); 7.68 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 43.9 (C-4); 55.4 (2OCH$_3$); 64.0 (C-5); 113.3, 114.0, 114.5, 118.8, 125.6, 127.1, 127.2, 128.9, 134.8, 145.3, 158.9, 160.1 (C Ar); 146.8 (C-3).

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