Asian Journal of Chemistry Vol. 22, No. 1 (2010), 589-592

Synthesis of 1,5-Diaryl-3-arylethenyl-2-pyrazolines Under Ultrasound Irradiation

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Synthesis of 1,5-diaryl-3-arylethenyl-2-pyrazolines *via* the reaction of 1,5-diaryl-1,4-pentadien-3-one and phenylhydrazine in glacial acetic acid was carried out in 32-80 % yields under ultrasound irradiation. This procedure has the advantages of mild conditions, short reaction time and high yield.

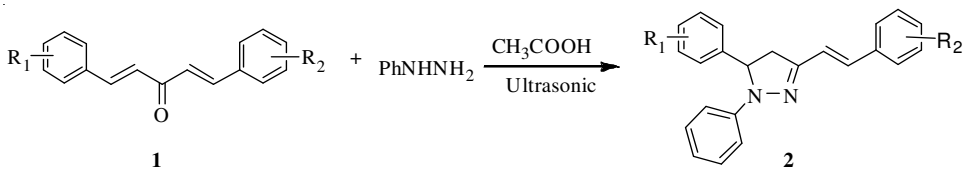
Key Words: 1,5-Diaryl-1,4-pentadien-3-one, Ultrasound irradiation, Pyrazoline, Synthesis.

INTRODUCTION

Pyrazoline derivatives have been found to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive and antidepressant activities[1-6]. Pyrazoline derivatives have better insecticidal activities and good optical properties[7,8]. They are widely used as fluorescent whitening agent for textiles and paper materials[9], hole-transporting medium in the electroluminescence system and photoelectric materials[10].

After the pioneering work of Fischer and Knoevenagel in the 19th century, the reaction of α,β-unsaturated aldehydes and ketones with phenylhydrazine is one of the important reactions for the preparation of 2-pyrazolines[11]. In 1966, 1,5-diphenyl-3-styryl-2-pyrazoline was prepared by the addition of phenylhydrazine to a boiling ethanolic solution of distyryl ketone[12]. In 1982, four of 1,5-diaryl-3-arylethenyl-2-pyrazolines were prepared *via* the condensation reaction of bischalcones with phenylhydrazine to give in 61-77 % yields in the presence of barium hydroxide in boiling ethanol for 12 h[13]. In 2005, Ignatenko *et al.*[14] used acetic acid instead of ethanol to give 1,5-diaryl-3-arylethenyl-2-pyrazolines in 32-72 % yields after standing the reaction mixture overnight. In spite of their potential utility, some of these methods suffer form longer reaction time and lower yields.

Ultrasound has increasingly been used in organic synthesis in the last three decades. A large number of organic reactions can be carried out under ultrasound irradiation in higher yield, shorter reaction time or milder conditions[15-17]. Herein, an efficient and practical procedure for the synthesis of 1,5-diaryl -3-arylethenyl-2-pyrazolines with bischalcones and phenylhydrazine in acetic acid under ultrasound irradiation (**Scheme-I**) is reported.



1 **2**

Scheme-I: Synthesis of 1,5-diaryl-3-arylethenyl-2-pyrazolines

EXPERIMENTAL

Phenylhydrazine was distilled prior to use. Melting points were uncorrected. ^{1}H NMR spectra were measured on Bruker AM-400S (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. MS were determined on a VG70E-HF spectrometer (EI, 70 eV). Sonication was performed in Shanghai Branson-BUG ultrasonic cleaner (with a frequency of 25 or 40 kHz and a nominal power 250 W).

Typical procedure: 1,5-Diaryl-1,4-pentadien-3-one was prepared according to literature[18]. Phenylhydrazine 108 mg (1 mmol), 1,5-diaryl-1,4-pentadien-3-one (**1a-k**, 1 mmol), glacial acetic acid (2 mL) were added into a 50 mL Pyrex flask. The mixture was irradiated in the ultrasonic cleaning bath at 50 ºC for 2 h. The solvent was removed under vacuum. The crude product was purified by column chromato-graphy on silica gel (200-300 mesh) eluted with petroleum ether or a mixture of petroleum ether and ethyl acetate to afford the product. The authenticity of compounds **2a-g** was established by their melting point compared with that reported in literatures[13-14,19-21], **2h-j** were established by ^{1}H NMR and MS.

1,5-Diphenyl-3-(4-phenyl-1,3-butadienyl)-2-pyrazoline (2h): m. p. 176-177 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.95 (dd, 1H, *J* = 6.6, 16.7 Hz, 4-H), 3.66 (dd, 1H, *J* = 12.6, 16.5 Hz, 4-H), 5.24 (dd, 1H, *J* = 6.8, 12.3 Hz, 5-H), 6.41 (dd, 1H, *J* = 10.7, 15.3 Hz, =CH), 6.78 (d, 1H, *J* = 15.8, =CH), 6.78-7.43 (m, 17H, Ph-H, =CH). MS (EI,70 eV) m/z (%): 350 (M^+, 100), 273 (61), 129 (6), 115 (10), 103 (3), 91 (43), 77 (21), 51 (9).

1,5-Diphenyl-3-(4-methylstyryl)-2-pyrazoline (2i): m.p. 120-121 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.31 (s, 3H, CH_3), 3.00 (dd, 1H, *J* = 6.3, 16.5 Hz, 4-H), 3.70 (dd, 1H, *J* = 12.3, 16.7 Hz, 4-H), 5.23 (dd, 1H, *J* = 6.5, 12.2 Hz, 5-H), 6.52 (dd, 1H, *J* = 5.3, 16.3 Hz, =CH), 7.00-7.43 (m, 15H, Ph-H, =CH). MS (EI, 70 eV) m/z (%): 338 (M^+, 98), 247 (43), 234 (11), 221 (2), 117 (16), 104 (11), 91 (100), 77 (57), 51 (18).

5-(2,4-Dichlorophenyl)-3-(2,4-dichlorostyryl)-1-phenyl-2-pyrazoline (2j): m.p. 156-158 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.92 (dd, 1H, *J* = 6.4, 16.8 Hz, 4-H), 3.84 (dd, 1H, *J* = 12.6, 16.4 Hz, 4-H), 5.61 (dd, 1H, *J* = 6.4, 12.4 Hz, 5-H), 6.85 (d, 1H, *J* = 16.4 Hz, =CH), 6.93-7.59 (m, 12H, Ph-H, =CH). MS (EI, 70 eV) m/z (%): 462 (M^+, 12), 317 (8), 159 (7), 121 (37), 90 (62), 77 (34), 51 (11).

RESULTS AND DISCUSSION

The effect of the reaction conditions on the reaction of bischalcone and phenylhydrazine under ultrasound irradiation was summarized in Table-1.

TABLE-1
EFFECT OF REACTION CONDITIONS ON SYNTHESIS OF
1,5-DIPHENYL-3-STYRYL-2-PYRAZOLINE UNDER ULTRASOUND*

Entry	Dibenzalacetone/ phenylhydrazine (mol)	Temp. (ºC)	Frequency (kHz)	Isolated yield (%)
1	1:1.0	30	25	64
2	1:1.0	30	40	67
3	1:1.0	40	40	70
4	1:1.0	50	40	75
5	1:1.1	50	40	64
6	1:1.2	50	40	74
7	1:1.0	30	Stir	57**

*The reaction time: 2 h, **Stirring without ultrasound.

As shown in Table-1, the effect of frequency of ultrasound irradiation on the reaction was not obvious. The yield with 40 kHz irradiation (entry 2) was better than that with 25 kHz irradiation for 2 h (entry 1). We also did the experiments in the absence of ultrasound, the reaction of 1,5-diphenyl-1,4-pentadien-3-one with phenylhydrazine was carried out in 57 % yield (entry 7) with stirring by refluxing for 2 h. It is apparent that the reaction can be finished in shorter time to give better yield under ultrasound irradiation. The reason may be the phenomenon of cavitation produced by ultrasound, which can cause reaction rapidly.

The effect of temperature on the reaction was also observed. The yield of **2a** was 67 % at 30 ºC under 40 kHz ultrasound irradiation (entry 2), when increasing the temperature to 40 or 50 ºC, the yield of **2a** was 70 and 75 %, respectively (entry 3, 4).

The influence of the molar ratio of 1,5-diphenyl-1,4-pentadien-3-one and phenylhydrazine on the reaction was investigated. When the molar ratio of 1,5-diphenyl-1,4-pentadien-3-one with phenylhydrazine was 1:1, 1,5-diphenyl-3-styryl-2-pyrazoline (**2a**) was obtained in 75 % yield (entry 4). By increasing the molar ratio to 1:1.1 or 1:1.2, the yield of **2a** increased to 64 and 74 % (entry 5,6). The results show that changing the molar ratio had not a significant effect on the yield of **2a**.

From the above results, the reaction conditions we chose were as follows: bischalcone (**1**, 1 mmol), phenylhydrazine (1 mmol), 50 ºC, glacial acetic acid (2 mL). Using this reaction system, we did a series of experiments for the reaction of 1,5-diphenyl-1,4-pentadien-3-one and phenylhydrazine under 40 kHz ultrasound irradiation at 50 ºC. The results were summarized in Table-2.

From the results shown in Table-2, it is deduced that the yields are, in general, similar or higher than those described in the literatures[13,14] under ultrasound irradiation. For example, in the presence of barium hydroxide in refluxing ethanol for 12 h, the **2a** and **2c** were obtained in 61 and 69 %, respectively[13]. However, the present method resulted **2a** and **2c** in 75 and 77 % yield, respectively (Table-2, entry 1, 3) within 2 h.

TABLE-2
SYNTHESIS OF 1,5-DIARYL-3-ARYLETHENYL-2-PYRAZOLINES UNDER ULTRASOUND

Entry	R_1	R_2	Product	Isolated yield, % (lit.)	m.p. (ºC) (lit.)
1	H	H	**2a**	75 (61[13], 69[14])	150-152(152-153)[13]
2	*p*-CH_3O	*p*-CH_3O	**2b**	76(75[13], 45[14])	162-163(159-163)[14]
3	*p*-Cl	*p*-Cl	**2c**	77(69[13], 72[14])	208-210(210-212)[14]
4	*p*-CH_3	*p*-CH_3	**2d**	67(76[13])	183-184(183-184)[13]
5	*p*-Br	*p*-Br	**2e**	80	229-230(227-228)[19]
6	*m*-Cl	*m*-Cl	**2f**	32	100-102[20](104)
7	*o*-CH_3O	*o*-CH_3O	**2g**	67	146-148[21](153-154.5)
8	H	-CH=CH-	**2h**	43(32[14])	176-177(106-108)[14]
9	H	*p*-CH_3	**2i**	59	120-121
10	2,4-Cl_2	2,4-Cl_2	**2j**	43	156-158
11	H	3,4-(OCH_2O)	**2k**	Trace	–

*Reaction time: 2 h.

In conclusion, an practical and convenient procedure for the preparation of 1,5-diaryl-3-arylethenyl-2-pyrazolines from some 1,5-diaryl-1,4-pentadien-3-one and phenylhydrazine under ultrasound irradiation is illustrated.

ACKNOWLEDGEMENT

The authors thank the Natural Science Foundation of Hebei Province, China, (B2006000969) for financial support.

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(*Received*: 6 March 2009; *Accepted*: 12 September 2009) AJC-7874