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A Convenient and Efficient Protocol for the Synthesis of 1,3,5-Triaryl-2-pyrazolines in Acetic Acid under Ultrasound Irradiation

ZHI-PING LIN* and JI-TAI LI

*Department of Biology and Chemistry
Baoding University, Baoding -071000, P. R. China
College of Chemistry and Environmental Science
Hebei University, Baoding -071002, P. R. China
zhiping888999@yahoo.com.cn

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Abstract: 1,3,5-Triaryl-2-pyrazolines were synthesized in acetic acid in high yields within 60-180 min under ultrasound irradiation at room temperature.

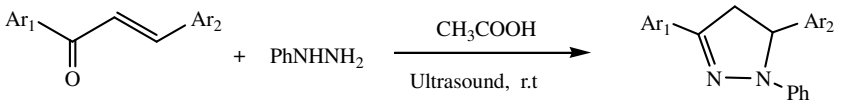
Keywords: 1,3,5-Triaryl-2-pyrazolines, Acetic acid, Synthesis, Ultrasound irradiation

Introduction

Pyrazoline derivatives have been found to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive, and antidepressantactivities[1-6]. As a new type of highly active insecticide, pyrazolines had very high activity towards coleopteran and lepidopteran insects[7]. The results of preliminary bioassay indicated that some of the compounds showed fungicidal and plant growth regulatory activities[8]. Benzothiazole compounds with byrazoline group or benximidazole group are new fluorescent compounds. The fluorescent compounds have been used in many fields, but their development has been slow[9,10]. The results from Zhang group indicate that the fluorescence quantum yield of compound with methoxy group is higher than that of compound with the substituents of *N,N*-dimethlyamino group[11].

Among of various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. A variety of methods have been reported for the preparation of this class of compounds. From 19th century, the reaction of α,β-unsaturated aldehydes and ketones with phenylhydrazine in acetic acid by refluxing became one of the most popular methods for the preparation of 2-pyrazolines[12]. Ultrasound has increasingly been used in organic synthesis in the last three decades. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under

ultrasound irradiation. The preparation of 1,3,5-triaryl-2-pyrazolines has been reported[13] in 2007, but the reaction was occurred at high temperature. In this paper we wish to report an efficient and practical procedure for the synthesis of 1,3,5-triaryl-2-pyrazolines with chalcones and phenylhydrazine in acetic acid under ultrasound irradiation at room temperature (Scheme 1). In this protocol, acetic acid is the reaction solvent and also is the catalyst.



1 **2** **3**

Scheme 1. Synthesis of 1,3,5-triaryl-2-pyrazolines under ultrasound irradiation

Experimental

Liquid substrates were distilled prior to use. Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE 600 (600 MHz) spectrometer using TMS as the internal standard and $CDCl_3$ as solvent. Elemental analyses were measured on a HERAEUS (CHNO, Rapid) analyzer. Sonication was performed in Shanghai BUG40-06 or BUG25-06 ultrasonic cleaner (with a frequency of 25 kHz, 40 kHz, 59 kHz and a nominal power 250 W).

Typical procedure for the preparation of 1,3,5-triaryl-2-pyrazolines

The chalcones was prepared by the reported method[14]. Chalcones (1, 2 mmol) and phenylhydrazine (2, 6 mmol) were dissolved in acetic acid (6 mL) in a 50 mL conical flask. The mixture was irradiated in the water bath of an ultrasonic cleaner for the period as indicated in Table 2. The reaction mixture was poured into crushed ice. The precipitate was separated by filtration, washed with water, and crystallized from ethanol to obtain the 1,3,5-triaryl-2-pyrazolines. The authenticity of compounds were established by their ^{1}H NMR, elemental analysis data and melting point.

3a ^{1}H NMR (DMSO): δ 3.13 (dd, J=7.2, 17.2 Hz, 1H), 3.82 (dd, J=12.4, 16.8 Hz, 1H), 5.26 (dd, J=7.2, 12 Hz, 1H) 6.80-7.75 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{18}N_2$: C 84.56, H 6.04, N 9.39; found C 84.60, H 6.14, N 9.37.

3b: ^{1}H NMR (DMSO): δ 3.14 (dd, J=7.2, 17.2 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.84 (dd, J=12.4, 16.8 Hz, 1H), 5.26 (dd, J=7.2, 12 Hz, 1H) 6.80-7.75 (m, 14H) ppm. Anal. calcd. for $C_{22}H_{20}N_2O$: C 80.48, H 6.09, N 8.54; found C 80.50, H 6.04, N 8.49.

3c: ^{1}H NMR (DMSO): δ 2.38 (s, 3H, CH_3), 3.15 (dd, J=7.2, 17.2 Hz, 1H), 3.85 (dd, J=12.4, 17.2 Hz, 1H), 5.27 (dd, J=6.8, 12 Hz, 1H) 6.77-7.75 (m, 14H) ppm. Anal. calcd. for $C_{22}H_{20}N_2$: C 84.62, H 6.41, N 8.97; found C 84.61, H 6.43, N 9.00.

3d: ^{1}H NMR (DMSO): δ 3.09 (dd, J=6.8, 17.2 Hz, 1H), 3.40 (dd, J=12.4, 17.2 Hz, 1H), 5.68 (dd, J=6.8, 12.4 Hz, 1H) 6.85-7.76 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Cl$: C 75.90, H 5.12, N 8.43; found C 75.83, H 5.23, N 8.45.

3e: ^{1}H NMR (DMSO): δ 3.08 (dd, J=6.8, 17.2 Hz, 1H), 3.40 (dd, J=12.4, 17.2 Hz, 1H), 5.68 (dd, J=6.8, 12.4 Hz, 1H) 6.83-7.77 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Cl$: C 75.90, H 5.12, N 8.43; found C 75.93, H 5.13, N 8.45.

3f: ^{1}H NMR (DMSO): δ 3.08 (dd, J=6.8, 17.2 Hz, 1H), 3.40 (dd, J=12.4, 17.2 Hz, 1H), 5.68 (dd, J=6.8, 12.4 Hz, 1H) 6.83-7.77 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2Cl$: C 75.90, H 5.12, N 8.43; found C 75.93, H 5.14, N 8.44.

3g: ^{1}H NMR (DMSO): δ 3.06 (dd, J=6.8, 17.1 Hz, 1H), 3.37 (dd, J=12.4, 17.2 Hz, 1H), 5.65 (dd, J=6.8, 12.4 Hz, 1H) 6.81-7.76 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2$: C 85.85, H 5.72, N 9.43; found C 85.81, H 5.73, N 9.44.

3h: ^{1}H NMR (DMSO): δ 3.01 (dd, J=7.8, 16.8 Hz, 1H), 3.78 (s, 3H, OCH_3), 3.82 (dd, J=12.4, 16.8 Hz, 1H), 3.84 (s, 3H, OCH_3), 5.26 (dd, J=7.2, 12 Hz, 1H) 6.80-7.75 (m, 13H) ppm. Anal. calcd. for $C_{23}H_{22}N_2O_2$: C 77.09, H 6.18, N 7.81; found C 76.69, H 6.14, N 7.70.

3i: ^{1}H NMR (DMSO): δ 3.15 (dd, J=7.2, 17.2 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.84 (dd, J=12.4, 16.8 Hz, 1H), 5.28 (dd, J=7.2, 12 Hz, 1H) 6.80-7.75 (m, 13H) ppm. Anal. calcd. for $C_{22}H_{19}N_2OCl$: C 72.93, H 5.25, N 7.73; found C 71.50, H 5.34, N 7.49.

3j: ^{1}H NMR (DMSO): δ 3.14 (dd, J=17.2, 17.2 Hz, 1H), 3.84 (dd, J=12.4, 17.2 Hz, 1H), 5.32 (dd, J=7.6, 12.4 Hz, 1H) 6.80-7.68 (m, 14H) ppm. Anal. calcd. for $C_{21}H_{17}N_2$: C 84.85, H 5.72, N 9.43; found C 84.87, H 5.74, N 9.46.

Results and Discussion

The effect of the reaction conditions on the reaction of chalcones and phenylhydrazine under ultrasound irradiation was summarized in Table 1. When the molar ratio of chalcones (**1**): phenylhydrazine (**2**) was 1:1, the yield of 1,3,5-triphenyl-2-pyrazoline was obtained in 88.1% yield (Table 1, Entry a). By increasing the molar ratio to 1:1.5, 1:2, and 1:3 the yields increased to 90.0, 93.5 and 95.6% respectively (Table 1, Entry b, c, d). The results showed that changing the molar ratio of 1:2 had a significant effect on the yield and the optimum molar ratio of chalcone: phenylhudrazine was 1:3. In the absence of ultrasound, the yield of 1,3,5-triphenyl-2-pyrazoline was only 77.0% (Entry l) by stirring at room temperature within 2 h. The data of entry b, c, d, h and j in Table 2 also verify the effect of ultrasound. It is apparent that the reaction can be finished in a shorter time to give better yield under ultrasound.

Table 1. Effect of reaction condition on synthesis of 1,3,5-triphenyl-2-pyrazoline within 2 h under ultrasound

Entry	Molar ratio of 1:2	Frequency, kHz	solvent	Isolated yield, %
a	1:1.0	25	HAc	88.1
b	1:1.5	25	HAc	90.0
c	1:2.0	25	HAc	93.5
d	1:3.0	25	HAc	95.6
e	1:3.0	40	HAc	94.6
f	1:3.0	59	HAc	92.6
g	1:3.0	25	EtOH	89.1
h	1:3.0	25	HAc:H_2O=3:1	55.0
i	1:3.0	25	HAc:H_2O=2:2	23.0
j	1:3.0	59	HAc:H_2O=1:3	trace
k	1:3.0	25	H_2O	0
l	1:3.0	Stir[a]	HAc	77.0

[a]*Stirred without ultrasound irradiation*

When the frequency was 25 kHz, the reaction gave the desired product in 95.6% yield within 2 h min (Entry d). Under 40 kHz and 59 kHz ultrasound irradiation, the 1,3,5-triphenyl-2-pyrazoline was obtained with 94.6% and 92.6% yield respectively (Entry e and f), thus indicating that different frequency of ultrasound irradiation had no significant effect on the yield of 1,3,5-triphenyl-2-pyrazoline.

We also carried out the reaction of chalcones and phenylhydrazine in acetic acid using different solvents under ultrasound. The results are listed in Table 1. The reaction in acetic acid proceeded smoothly under ultrasound irradiation, while not so efficient in the solvent including water. So the study continued to be done using acetic acid. And the most important in our protocol, no other catalyst need to add during the reaction. The acetic acid is the reaction solvent and also is the catalyst.

From the above results, the optimum reaction conditions were chosen; chalcone (1), 2 mmol, phenylhydrazine (2), 6 mmol and acetic acid 6 mL. Under this reaction system, a series of experiments for synthesis of 1,3,5-triaryl-2-pyrazolines under 25 kHz ultrasound irradiation were performed. The results are summarized in Table 2.

Table 2. Synthesis of 1,3,5-triaryl-2-pyrazolines in acetic acid under ultrasounics at room temparature

Entry	Ar_1	Ar_2	Time, min	Yield, %	m.p.Found(Lit.) ^oC [Ref.]
a	C_6H_5	C_6H_5	120	95.6	134-135(134-135)[6]
b	C_6H_5	4-$CH_3OC_6H_4$	110	99.0	110-111(110-112)[13]
				85.5[a]	-
c	C_6H_5	4-$CH_3C_6H_4$	90	99.0	127-129(128-130)[13]
				80.1[a]	-
d	C_6H_5	4-ClC_6H_4	120	94.9	134-135(135-136)[13]
				79.8[a]	-
e	C_6H_5	3-ClC_6H_4	100	87.8	134-135(134-136)[13]
f	C_6H_5	2-ClC_6H_4	100	84.9	134-135(135-136)[13]
g	C_6H_5	3-BrC_6H_4	180	18.3	141-142(141-143)[13]
h	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	60	97.9	139-141(139-140)[15]
				81.3[a]	-
i	4-ClC_6H_4	4-$CH_3OC_6H_4$	60	95.5	158-159(160-161)[16]
j	4-ClC_6H_4	C_6H_5	90	89.5	142-144(143-145)[13]
				75.9[a]	-
k	C_6H_5	4-$NO_2C_6H_4$	180	trace	-

[a]*The reaction was occurred without ultrasound*

From the Table 2 data, it seems that either electron-donating substituents or electron-withdrawing substituents in the benzene ring have no significant effects on the yields in this system. 1,3-Diphenyl-5-(4-methylphenyl)-2-pyrazoline and 1,3-diphenyl-5-(4-chlorophenyl) -2-pyrazoline can obtain in 88% and 86% yield as per literature report, but it is higher to 99.0% and 94.9% in present system at room temperature. Moreover, acetic acid both is the reaction solvent, and is the catalyst.

In conclusion, we have found an efficient and practical procedure for the synthesis of some 1,3,5-triaryl-2-pyrazolines *via* the condensation of chalcones and phenylhydrazine under ultrasound irradiation at room temperature.

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References

1. Patel V M and Desai K R, *Arkivoc,* 2004, **(i)**, 123.
2. Chen Y, Lam Y L and Lai Y H, *Org Lett.,* 2003, **5**, 1067.
3. Parmar S S, Pandey B R, Dwivedi C and Harbinson R D, *J Pharm Sci.,* 1974, **63**, 1152.
4. Soni N, Pande K, Kalsi R, Gupta T K, Parmar S S and Barthwal J P, *Res Commun Chem Pathol Pharm.,* 1987, **56(1)**, 129-132.
5. Turan-Zitouni G, Chevallet P, Kilic F S and Erol K, *Eur J Med Chem.,* 2000, **35(6)**, 635-641.
6. Rajendra Y P, Lakshmana R A, Prasoona K, Murali K and Ravi K P, *Bioorg Med Chem Lett.,* 2005, **15**, 5030-5034.
7. Salgado V L, *Pesti Sci*., 1990, **28**, 389.
8. Franck-Neumann M and Miesch M, *Tetrahedron Lett*, 1982, **23**, 1409.
9. Jin M, Lu Ran, Chuai X H, Zhang Y H and Zhao Y Y, *Chem J Chin Univ.,* 2002, **23**, 466.
10. Zhu W H and Tian H, *Prog Chem*., 2002, **14**, 18.
11. Zhang X H, Wu S K, Gao Z Q, Li Z S and Li S T, *Acta Chimica Sinaca*, 2000, **58**, 293.
12. Levai A, *ARKIVOC,* 2005, **(ix)**, 344.
13. Li J T, Zhang X H and Lin Z P, *Beilstein J Org Chem.,* 2007, **3**, 13.
14. Li J T, Yang W Z, Wang S X, Li S H and Li T S, *Ultrason Sonochem.,* 2002, **9**, 237-239.
15. Ando W, Sato R, Yamashita M, Akasaka T and Miyazaki H, *J Org Chem.,* 1983, **48**, 542.
16. Kidwai M, Kukreja S and Thakur R, *Lett Org Chem.,* 2006, **3**, 135.