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Short Communication

A convenient and efficient protocol for the synthesis of 5-aryl-1,3-diphenylpyrazole catalyzed by hydrochloric acid under ultrasound irradiation

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ABSTRACT

The synthesis of 5-aryl-1,3-diphenylpyrazole *via* the reactions of 3-aryl-2,3-epoxy-1-phenyl-1-propanone with phenylhydrazine was carried out in 69–99% yields at room temperature under ultrasound irradiation. This method provides several advantages such as operational simplicity, higher yield and environment friendly.

1. Introduction

Aryl pyrazoles are ubiquitous substructures with important biological activity and pharmacological properties [1], including antimicrobial [2], anti-inflammatory [3], hypoglycemic [4], antihypertensive [5] and analgesic [6] properties. As a part of drug development program, numerous methods for the synthesis of 1,3,5-triarylpyrazole have been reported [7–12]. Azarifar and Maleki synthesized 1,3,5-triarylpyrazole in 90–96% yields from the oxidative aromatization of 3,5-diaryl-1-phenyl-2-pyrazoline catalyzed by tricholoroisocyanuric acid (TCCA) in CH_2Cl_2 under microwave irradiation [8]. Heller and Natarajan reported the condensation reaction of 1-(4-methoxyphenyl)-3-(4-nitrophenyl)propane-1,3-dione and phenylhydrazine in toluene catalyzed by LiHMDS and the yield was only 43% [9]. Deng et al. showed that the reaction of (E)-1-(4-chlorobenzylidene)-2-phenylhydrazine and (E)-5-(2-nitrovinyl)-benzo[*d*][1,3]dioxole was refluxed for 4 days in H_2O-DMF to give 5-(benzo[d][1,3]dioxol-5-yl)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole in 42% yield [10]. Ahlström et al. used 4-sulfamoylphenyl hydrazine hydrochloride and 3-(4-methylphenyl)-2,3-epoxy-1-phenylpropanone to prepare the corresponding 4-[5-(4-methylphenyl)-3-phenyl-1H-pyrazol-1-yl]-benzenesulfonamide in 21% yield under microwave [11]. Liu et al. reported the synthesis of 1,3,5-triarylpyrazoles from acid chlorides, terminal alkynes and hydrazines *via* a coupling and cyclocondensation sequence in 15–85% yields [12]. However, in spite of their potential utility, some of the reported methods suffer from draw-backs such as lower yield, expensive transition metal oxidant, use of toxic organic solvent and complexity of work-up. Thus, the development of a simple, efficient and green method for the preparation of 5-aryl-1,3-diphenylpyrazole is an active area of research.

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades [13], compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation [14]. Mamaghani and Dastmard have reported the conversion of Baylis–Hillman adducts into 1,5-diarylpyrazoles in good yields under ultrasound irradiation [15]. Continuing our investigations in synthesis of 5-aryl-1,3-diphenylpyrazole [16], we wish to report an efficient and facile procedure for the synthesis of 5-aryl-1,3-diphenylpyrazole under ultrasound irradiation (Scheme 1).

2. Methods

3-Aryl-2,3-epoxy-1-phenyl-1-propanone was prepared according to method reported in literature [17]. Melting points was uncorrected. Sonication was performed in Shanghai BUG40-06 ultrasonic cleaner (with a frequency of 40 kHz and a nominal power 250 W). The ^{1}H NMR spectras were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal

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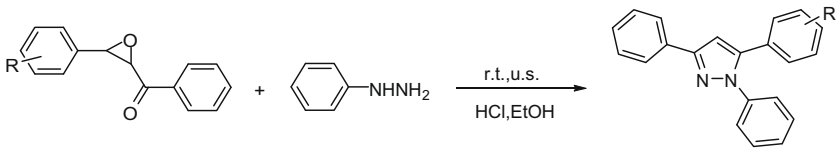

1a-j 2a-j

Scheme 1. Synthesis of 5-aryl-1,3-diphenylpyrazole.

standard and $CDCl_3$ as solvent and Bruker AVANCE 300 (300 MHz) spectrometer using TMS as internal standard and DMSO as solvent. The ^{13}C NMR spectras were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and DMSO as solvent. LC–MS were determined on SHIMADZU (LCMS-2010EA, UVD/ELSD) using CH_3CN and H_2O (0.05% TFA) as mobile phase, the column type is Shim_pack XR-ODS with length 50 mm and internal 3 mm, the flow rate is 1 mL/min, and the gradient is as follows. Time (min.)/CH_3CN (%): 0/15, 1.70/100, 3.20/100, 3.33 /10, 3.60/ stop.

2.1. Typical procedure for the preparation of 5-aryl-1,3-diphenylpyrazole

A 25 mL round-bottomed flask was charged with **1** (1.0 mmol), phenylhydrazine (0.130 g, 1.2 mmol) and ethanol (2 mL), in the presence of catalytic amount of 3 mol/L aqueous hydrochloric acid (0.2 equiv). The reaction flask was located in the cleaner bath, where the surface of reactants is slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. The mixture was irradiated at r.t. for the period as indicated in Table 2. The completion of reaction was monitored by TLC (petroleum ether:ethyl acetate, 10:1). After the completion of the reaction, the solvent was removed by evaporation under reduced pressure to give the crude products, then the crude products were purified by column chromatography on silica gel (200–300 mesh) eluted with a mixture of petroleum ether and ethyl acetate to afford the product **2a–j.** The authenticity of the products **2b** and **2c** was established by their ^1H NMR, ^{13}C NMR, MS; the rest known compounds were established by their melting points compared with that reported in literatures [7,8,16–20].

Table 1
The effect of the amount of hydrochloric acid on the yield of 1,3,5-triphenylpyrazole under ultrasound irradiation.

Entry	Substrate/hydrochloric acid, molar ratio	Time (min)	Isolated yield (%)
1	1:0.1	43	84
2	1:0.2	45	89
3	1:0.3	14	82

2.1.1. Compound **2b**

5-(2-Nitrophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 65–67 °C; *m/z* (ES): 342 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ_H: 6.79 (1H, s, pyrazole-H), 7.25–7.62 (10H, m, Ar–H), 7.91 (4H, d, *J* = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO): 152.0, 149.1, 140.3, 139.9, 134.6, 133.7, 133.3, 131.7, 130.0, 129.6, 129.0, 128.5, 126.3, 125.7, 125.5, 124.9, 106.9 ppm.

2.1.2. Compound **2c**

5-(4-Methylphenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 115–117 °C; *m/z* (ES): 310 $[M+H]^+$; ^1H NMR (300 MHz, DMSO): δ_H: 2.31 (3H, s, CH_3–H), 7.13 (1H, s, pyrazole-H), 7.19 (4H, s, Ar–H), 7.33–7.49 (8H, m, Ar–H), 7.92 (2H, d, *J* = 6.9 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO): 151.8, 145.1, 140.8, 138.8, 133.7, 130.0, 129.9, 129.6, 129.2, 128.8, 128.5, 128.0, 126.3, 126.1, 105.9, 21.6 ppm.

3. Results and discussion

In order to improve the yield, the effects of the catalyst on the condensation of 2,3-epoxy-1, 3-diphenyl-1-propanone with phenylhydrazine were examined under ultrasound irradiation.

Table 2
Condensation of 3-aryl-2,3-epoxy-1-phenyl-1-propanones and phenylhydrazine.

Entry	Ar	Time (min)	Product	Method[a]	Isolated yield (%)	m.p., °C (lit.)
a	C_6H_5	45	2a	A	89	138–139 (138–138.5) [18]
		45		B	69	
		240		C	42	
b	2-$NO_2C_6H_4$	60	2b	A	95	65–67 (126–128) [8]
		60		B	73	
		240		C	42	
c	4-$CH_3C_6H_4$	70	2i	A	69	115–117 (142–143) [20]
		70		B	58	
		240		C	20	
d	4- ClC_6H_4	80	2 g	A	85	103–105 (104–105) [7b]
		80		B	73	
e	2-$CH_3OC_6H_4$	80	2j	A	83	142–144 (145) [16]
		240		C	13	
f	3-$NO_2C_6H_4$	80	2c	A	75	130–132 (130) [19]
g	4-$NO_2C_6H_4$	165	2d	A	80	140–141 (139–141) [8]
h	2-ClC_6H_4	45	2e	A	91	Yellow liquid [16]
i	3-ClC_6H_4	80	2f	A	86	95–97 (93–95) [8]
j	3,4-$Cl_2C_6H_3$	60	2 h	A	99	82–84 (83–84) [16]

[a] Method, reaction temperature, r.t.; the molar ratio of 1 and HCl, 1:0.2; (A) ultrasound irradiation; (B) stirring and (C) lying at 8 °C [18].

As shown in Table 1, with the increasing of the molar ratio of 2,3-epoxy-1,3-diphenyl -1-propanone and hydrochloric acid from 1:0.1 to 1:0.2, higher yield (89%) was achieved in the similar reaction time (**Entry 2**). When increasing the molar ratio to 1:0.3, the conversion was completed in 14 min, but the yield was reduced to 82% (**Entry 3**). We deduce that some of the phenylhydrazine may combine with hydrochloric acid to produce the inert phenylhydrazine hydrochloride with the increasing of the concentration of hydrochloric acid, thus, the yield of **2a** could hardly be increased. The results showed that changing the molar ratio of **1a** with hydrochloric acid had a significant effect on the yield of **2a**, and the optimum molar ratio of **1a** and hydrochloric acid was 1:0.2.

In order to verify the effect of ultrasound irradiation, we have performed the reaction of 3-aryl-2,3-epoxy-1-phenyl-1-propanone and phenylhydrazine catalyzed by hydrochloric acid by stirring in the absence of sonication, the yields of 5-ary-1,3-diphenyllpyrazole, for example, **2b** was obtained in 73%, while under ultrasound **2b** was obtained in 95% yield (Table 2, **Entry b**). It showed that ultrasound irradiation improved the result.

We also repeated the experiment reported in Ref. [18], put 3-(2-nitrophenyl)-2,3-epoxy-1-phenyl-1-propanone and phenylhydrazine into the mixture of methanol, chloroform and acetic acid, and then lying at 8 °C for 240 min. This reaction gave **2b** in 42% yield which was not only lower than that reported in reference (86%), but also lower than the result of our method (95%) (Table 2, **Entry b).** The method has many other disadvantages, such as hardly controlled temperature, longer reaction time, and the use of toxic organic solvent and so on.

From the results above, a typical experimental procedure was chosen: 3-aryl-2,3-epoxy-1-phenyl-1-propanone (**1**, 1.0 mmol), phenylhydrazine (0.130 g, 1.2 mmol), ethanol (2 mL) and hydrochloric acid (0.2 equiv). Using this system, we did a series of experiments to prepare 5-aryl-1,3-diphenylpyrazole under ultrasound irradiation. The results were summarized in Table 2.

As shown in Table 2, the condensation of 3-aryl-2,3-epoxy-1-phenyl-1-propanone with phenylhydrazine affords product **2** in good yields, which are, in general, similar or higher than those described in literatures [7–12]. It is also worth noting that the electronic effects of substituents on the benzene ring seem to have no effect on the yields of products.

Compared with other reported methods, we can deduce that the present method represented a better procedure with main advantages of operational simplicity, higher yields, mild reaction conditions and environment friendly, which make it a useful and attractive process for the synthesis of these compounds.

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

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