Solvent-Free Synthesis of 1,3-Diphenyl-5-arylpyrazole Derivatives

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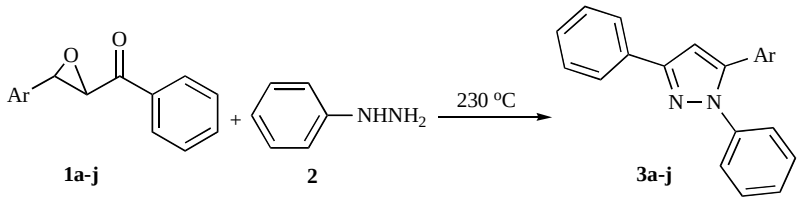
Received December 29, 2008: Revised April 16, 2009: Accepted April 23, 2009

Abstract: The synthesis of 1,3-diphenyl-5-arylpyrazoles *via* the reactions of 2,3-epoxy-1-phenyl-3-aryl-1-propanones with phenylhydrazine was carried out in 48-84% yields at 230 ^{o}C under solvent-free condition within 1.5 h. This method provides several advantages such as operational simplicity, higher yield and solvent-free.

Keywords: cyclization, 1,3-diphenyl-5-arylpyrazole, synthesis, solvent-free reaction, heterocycles.

INTRODUCTION

Aryl pyrazoles are ubiquitous substructures with important biological activity and pharmacological properties [1], including antimicrobial [2], anti-inflammatory [3], hypoglycemic [4], anti-hypertensive [5] and analgesic [6] properties. As a part of drug development program, numerous methods for the synthesis of 1,3,5-triarylpyrazoles have been reported [7-12]. However, in spite of their potential utility, some of the reported methods suffer from draw-backs such as longer reaction time, 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 1,3-diphenyl-5-arylpyrazoles is an active area of research.



Scheme 1. Synthesis of 1,3-diphenyl-5-arylpyrazoles.

One of the greatest environmentally problematic aspects of organic synthetic chemistry is the use of solvent. The best way is to eliminate the use of solvent [13]. Refraining from the use of solvents in organic synthesis has led to improved results and milder synthetic procedures in some cases. Moreover, solvent-free thermal reactions are more important for practical synthetic processes in the industry [14,15].

All of the results stated above spur us to study the possibility of solvent-free synthesis of 1,3-diphenyl-5-arylpyrazoles. Herein, we wish to report a simple and efficient method for synthesis of 1,3-diphenyl-5-arylpyrazoles under the solvent-free condition (Scheme **1**).

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RESULTS AND DISCUSSION

Under solvent-free condition, the effect of the reaction conditions on the condensation of 2,3-epoxyl-1,3-diphenyl-1-propanone (**1a)** and **2** was observed. The results are summarized in Table **1**.

As shown in Table **1** (Entries **1-5),** the yield of **3a** increased from 48% to 82 % by changing the temperature from 170 ^{o}C to 230 ^{o}C. When the temperature was 240 ^{o}C, the **3a** was obtained in 77 % yield. The results showed that 230 ^{o}C was the appropriate temperature for this reaction.

The molar ratio of substrate and reagent showed crucial effect on the reaction yield. When the molar ratio of **1a** and **2** was 1:1.1, **3a** was obtained in 82% yield (Entry **4**). When the molar ratio was 1:1 or 1:1.2, the yield of **3a** was 70% and 82% respectively (Entries **6** and **7**).

In order to examine the effect of reaction times, the reaction of **1a** and **2** was selected as a model reaction. It was found that when the reaction time was 1.5 h, the yield of **3a** was 82%, and prolonged reaction time had little effect on yield.

From the results above, the reaction conditions we chose were as follows: the ratio of **1a** and **2** was 1:1.1**,** the temperature was 230 ^{o}C and the reaction time was 1.5 h. Using this reaction system, a series of 1,3-diphenyl-5-arylpyrazoles were prepared. The results are summarized in Table **2**.

From these results, we can deduce that the yields are in general, similar or higher than those described in literatures [7-12]. Compared with other reported methods, the main

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Table 1. The Effect of Reaction Conditions on the Condensation of 1a and **2**

Entry	Molar ratio[a]	Time (h)	Temp. (°C) [b]	Isolated yield (%)
1	1:1.1	2	170	48
2	1:1.1	2	190	55
3	1:1.1	2	210	74
4	1:1.1	2	230	82
5	1:1.1	2	240	77
6	1:1	2	230	70
7	1:1.2	2	230	82
8	1:1.1	1.5	230	82
9	1:1.1	2.5	230	82
10	1:1.1	3	230	79

[a]Molar ratio of **1a** and **2**.
[b]The temperature of oil bath.

Table 2. Condensation of 2,3-Epoxy-1-phenyl-3-aryl-1-propanones and Phenylhydrazine[a]

Entry	Ar	Product	Isolated yield (%)	m.p. (°C) (lit.)
a	C_6H_5	**3a**	82	138-139(138-138.5) [17]
b	3-$NO_2C_6H_4$	**3b**	56	128-130(130) [18]
c	4-$NO_2C_6H_4$	**3c**	48	137-139(139-141) [8]
d	2-ClC_6H_4	**3d**	84	yellow liquid
e	3-ClC_6H_4	**3e**	75	91-93(93-95) [8]
f	4-ClC_6H_4	**3f**	81	106-108(104-105) [7b]
g	2, 4- $Cl_2C_6H_3$	**3g**	77	yellow liquid
h	3, 4- $Cl_2C_6H_3$	**3h**	81	83-84
i	2-$CH_3OC_6H_4$	**3i**	82	145(116-117) [7b]
j	3-BrC_6H_4	**3j**	79	107

[a]Reaction temperature, 230 °C; reaction time,1.5 h ; the molar ratio of **1a** and **2**, 1:1.1.

advantages of the procedure are operational simplicity, higher yields and solvent-free, 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 1,3-diphenyl-5-arylpyrazoles *via* the condensation of 2,3-epoxy-1-phenyl-3-aryl-1-propanones and phenylhydrazine under a solvent-free condition.

EXPERIMENTAL

2,3-Epoxy-1-phenyl-3-aryl-1-propanones were prepared according to literature [16]. Melting points was uncorrected. The ^{1}H NMR spectras were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. MS were determined on SHIMADZU (LCMS-2010EA, UVD/ELSD) using CH_3CN & 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.

Typical Procedure for the Preparation of 1,3-Diphenyl-5-arylpyrazoles

A 25 mL round-bottomed flask was charged with **1a-j** (1.0 mmol), and **2** (0.119 g, 1.1 mmol). The mixture was heated at 230 °C. After completion of the reaction (the reaction was followed by TLC), the reaction mixture was purified by column chromatography on silica gel (200-300 mesh) eluted with a mixture of petroleum ether and ethyl acetate to afford the product **3a-j**, The authenticity of the products **3d, 3g, 3h, 3i** and **3j** were established by their ^{1}H NMR, MS; the rest known compounds were established by their MS and melting points compared with that reported in literatures [7, 8, 17,18].

Compound 3a

1,3,5-triphenyl-1H-pyrazole, yellow solid, m.p.138-139 °C; *m/z* (ES): 297 $[M+H]^+$.

Compound 3b

5-(3-nitrophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 128-130 °C; *m/z* (ES): 342 $[M+H]^+$.

Compound 3c

5-(4-nitrophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 137-139 ^{o}C; *m/z* (ES): 342 $[M+H]^{+}$.

Compound 3d

5-(2-chlorophenyl)-1,3-diphenyl-1H-pyrazole, yellow liquid; *m/z* (ES): 331 $[M+H]^{+}$; ^{1}H NMR (400MHz, $CDCl_3$): δ_H6.86 (1H, s, pyrazole-H), 7.25-7.45 (12H, m, Ar-H), 7.95 (2H, d, *J*=7.2Hz, Ar-H).

Compound 3e

5-(3-chlorophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 91-93 ^{o}C; *m/z* (ES): 331 $[M+H]^{+}$.

Compound 3f

5-(4-chlorophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 106-108 ^{o}C; *m/z* (ES): 331 $[M+H]^{+}$.

Compound 3g

5-(2,4-dichlorophenyl)-1,3-diphenyl-1H-pyrazole, yellow liquid; *m/z* (ES): 365 $[M+H]^{+}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.84 (1H, s, pyrazole-H), 7.17-7.45 (11H , m, Ar-H),7.93 (2H, d, *J*=7.1Hz, Ar-H).

Compound 3h

5-(3,4-dichlorophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 83-84 ^{o}C; *m/z* (ES): 365 $[M+H]^{+}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.83 (1H, s, pyrazole-H), 7.00(1H, dd, J_1=8.3Hz, J_2=1.7Hz, Ar-H), 7.33-7.45 (11H, m, Ar-H),7.89 (2H, d, *J*=7.4Hz, Ar-H).

Compound 3i

5-(2-methoxyphenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 145 ^{o}C; *m/z* (ES): 327 $[M+H]^{+}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.40 (3H, s, OCH_3), 6.81 (2H, S, Ar-H), 7.01(1H, t, *J*=7.4Hz, pyrazole-H**)** 7.01-7.45 (10H, m, Ar-H),7.94 (2H, d, *J*=7.3Hz, Ar-H).

Compound 3j

5-(3-bromophenyl)-1,3-diphenyl-1H-pyrazole, yellow solid, m.p. 107 ^{o}C; *m/z* (ES): 375 $[M+H]^{+}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.85 (1H, s, pyrazole-H),7.12-7.19 (2H, m, Ar-H), 7.34-7.52 (10H, m, Ar-H),7.91 (2H, d, *J*=7.3Hz, Ar-H).

ACKNOWLEDGEMENTS

The project was supported by Natural Science Foundation of Hebei Province (B2006000969), China.

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