A NEW METHOD TO SYNTHESIZE 3,5-DIARYLPYRAZOL DERIVATIVES

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ABSTRACT

Twelve 3, 5-diarylpirazoles have been synthesized by microwave-assisted condensation reaction in a short and concise manner using various aromatic aldehydes and aromatic ketones as starting materials. The corresponding products were obtained in good yields (87-96%). All products were identified by MS, ¹H NMR, ¹³C NMR and elemental analysis. The advantages of this novel protocol include the excellent yield, operational simplicity, short time and the avoidance of the use of expensive catalysts.

Keywords: 2, 4, 6-Triarylpyrylium salts, 3,5-Diarylpirazoles, Microwave irradiation.

INTRODUCTION

Pyrazoles are important nitrogen-containing five-membered heterocyclic compounds¹⁻³ and numerous compounds containing pyrazole have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial activity⁴. Moreover, metal complexation to the pyrazole heterocycle could offer a straightforward way to couple the effect of a metal bound to one heterocyclic nitrogen with the ability of the N-H to donate a proton or hydrogen bond⁵. Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds⁶⁻⁷.

Meanwhile, high-speed synthesis under microwave irradiation conditions has attracted a considerable amount of attention⁸⁻⁹, and some important reviews in the study of microwave assisted organic synthesis have been published¹⁰, the scope of applications is very extended and concerns a wide spectrum of organic synthesis procedures including, for instance, heterocyclic, organometallic, radio photo and combinatorial chemistries¹¹⁻¹².

In recent years, Wang et al have developed a general synthesis of 2,4,6-triarylpyridiums, which were important oxygen-containing building blocks and their use in heterocyclic preparations (e.g., pyridines, thiophenes, furans and diazepines) has been extensively described¹³⁻¹⁴.

In continuation of our efforts to develop novel synthetic routes for carbon-carbon and carbon-heteroatom bond formations and heterocycles using 2,4,6-triarylpyridiums as starting materials, we have been interested in developing new, more efficient, and synthetically useful reactions for the synthesis of biologically active molecules via microwave acceleration. Thus, the aim of this work is to demonstrate the advantages obtained by the use of microwave irradiation for the synthesis of 3,5-diarylpirazoles.

EXPERIMENTAL

¹H NMR spectra (200MHz) were recorded using a Bruker AC-E 200 MHz, 400 MHz spectrometer in CDCl₃, CD₃COCD₃, DMSO-*d*₆ with TMS as an internal standard. Mass spectra measurements were performed on a QP-1000A GC-MS spectrometer by EI ionization at 70 eV. Purification of products was performed via flash chromatography with 200–400 mesh silica gel [petroleum ether (bp 60–90 °C)–EtOAc, 5:1]. The chemicals were obtained from commercial sources.

General experimental procedure

We prepared a series of pyrylium salts in the absence of solvent under microwave irradiation. Then, 1,3,5-triphenyl-2-pentene-1,5-diketone were prepared by the reaction of pyrylium salts with NaOAc. Next, 1,3,5-triphenyl-2-pentene-1,5-diketone (0.1mmol) was added in an open flask, followed by the addition of hydrazine hydrate (1mmol) and acetic acid (1.2 ml). Then the mixture was irradiated in microwave (375W) in an open flask for 5min. After the reaction was completed, the reaction mixture was left to room temperature, then water was added obtaining a white precipitate, the solid was isolated by filtration and washed with water. The product was purified by recrystallization once or twice from dilute ethanol or by flash chromatography with 200–400 mesh silica gel [petroleum ether (bp 60–90 °C)–EtOAc, 5:1]. The reactions are shown in **Scheme 1** and the results are summarized in **Table 1**

Scheme 1. The synthetic route of the title compounds.

Table 1. Synthesis of 3, 5-diarylpirazoles.

Entry	R ¹	R ²	Yield*(%)	Time(min)/power(W)
5a	H	H	96	5/375
5b	H	4-CH ₃	97	5/375
5c	H	4-Cl	89	6/375
5d	H	4-Br	94	7/375
5e	4-CH ₃	H	95	5/375
5f	4-CH ₃	4-CH ₃	91	5/375
5g	4-CH ₃	4-Cl	90	5/375
5h	4-CH ₃	4-Br	92	5/375
5i	4-Cl	H	88	6/375
5j	4-Cl	4-CH ₃	93	6/375
5k	4-Cl	4-Cl	92	7/375
5l	4-Cl	4-Br	87	7/375

*The yield is based on the compound **4**

Taking the reaction of 1,3,5-triphenyl-2-pentene-1,5-diketone with hydrazine hydrate as an example, we investigated the effect of the power and time of microwave irradiation. The results are summarized in the **Table 2** and **Table 3**. The results shown that the title compounds can rapidly be obtained in 375W power for 5 min.

Table 2. Effect of the power of MWI on synthesis of 3, 5-diarylpyrazoles.

Power (W)	150	225	300	375	450
Yield (%)	46	72	85	96	92

Table 3. Effect of the time of MWI on synthesis of 3, 5-diarylpyrazoles.

Time (min)	2	3	4	5	6
Yield (%)	58	75	90	96	96

From the tables, we found the optimum condition of the reaction: the time of MWI is 5~7min, the power of MWI is 375W.

Spectral data for compounds

3,5-diphenyl-1H-pyrazole

White crystals, mp 199-201°C (lit.^[15] 199°C); ¹H NMR (200MHz, CDCl₃) δ = 7.75-7.69 (m, 5H), 7.45-7.24 (m, 5H), 6.84 (s, 1H); ¹³C NMR (100MHz, CDCl₃) δ = 148.75, 130.99, 128.90, 128.42, 125.66, 100.22; MS (m/e, %): 220 (M⁺, 80.38), 191 (M⁺-N-NH, 13.87), 77 (C₆H₅, 32.16); Anal Calcd for C₁₅H₁₂N₂: C, 81.79; H, 5.49; N, 12.72; Found: C, 81.88; H, 5.163; N, 12.92.

5-phenyl-3-p-tolyl-1H-pyrazole

White crystals, mp 179-181°C (lit.^[16] 183-184°C); ¹H NMR (200MHz, CD₃COCD₃) δ = 12.59 (b, 1H), 8.01-7.36 (m, 9H), 7.19 (s, 1H), 2.47 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ = 149.19, 148.06, 138.28, 129.66, 128.84, 127.70, 126.12, 100.52; MS (m/e, %): 234 (M⁺, 100), 205 (M⁺-N-NH, 6.15), 91 (C₆H₅CH₂, 17.58), 77 (C₆H₅, 62.10); Anal Calcd for C₁₆H₁₄N₂: C, 82.02; H, 6.024; N, 11.95; Found: C, 81.81; H, 5.833; N, 12.04.

3-(4-chlorophenyl)-5-phenyl-1H-pyrazole

White crystals, mp 218-220°C (lit.^[17] 217°C); ¹H NMR (200MHz, CDCl₃) δ = 7.68-7.41 (m, 9H), 6.83 (s, 1H); ¹³C NMR (100MHz, CD₃COCD₃) δ = 149.19, 148.06, 138.28, 129.66, 128.84, 127.70, 126.12, 100.52; MS (m/e, %): 256 (M⁺+2, 34.86), 254 (M⁺, 100), 225 (M⁺-N-NH, 9.43), 111 (C₁₀H₇, 48.48), 77 (C₆H₅, 38.64); Anal Calcd for C₁₅H₁₁ClN₂: C, 70.73; H, 4.35; N, 10.99; Found: C, 70.67; H, 4.28; N, 11.08.

3-(4-bromophenyl)-5-phenyl-1H-pyrazole

White crystals, mp 217-218°C (lit.^[17] 215°C); ¹H NMR (200MHz, CDCl₃) δ = 7.66-7.35 (m, 9H), 6.77 (s, 1H), MS (m/e, %): 300 (M⁺+2, 93.68), 298 (M⁺, 100), 269 (M⁺-N-NH, 7.14), 77 (C₆H₅, 16.49).

3-phenyl-5-p-tolyl-1H-pyrazole

White crystals, mp 180-182°C (lit.^[16] 183-184°C); ¹H NMR (200MHz, CD₃COCD₃) δ = 12.54 (b, 1H), 7.97-7.28 (m, 9H), 7.14 (s, 1H), 2.42 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ = 149.08, 148.35, 138.22, 131.39, 129.53, 128.80, 128.19, 128.09, 125.65, 125.53, 99.84, 21.26; MS (m/e, %): 234 (M⁺, 100), 205 (M⁺-N-NH, 6.15), 91 (C₆H₅CH₂, 17.58), 77 (C₆H₅, 62.10); Anal Calcd for C₁₆H₁₄N₂: C, 82.02; H, 6.024; N, 11.95; Found: C, 81.72; H, 5.627; N, 12.44.

3,5-dip-tolyl-1H-pyrazole

White crystals, mp 237-238°C; ¹H NMR (200MHz, CD₃COCD₃) δ = 12.39 (b, 1H), 7.78-7.23 (m, 8H), 7.02 (s, 1H), 2.389 (s, 6H); ¹³C NMR (100MHz, CDCl₃) δ = 150.31, 148.73, 138.50, 129.56, 127.90, 125.68, 99.82, 21.29; MS (m/e, %): 248 (M⁺, 100), 233 (M⁺-CH₃, 2.35), 219 (M⁺-N-NH, 3.71), 91 (C₆H₅CH₂, 5.01), 77 (C₆H₅, 9.64); Anal Calcd for C₁₇H₁₆N₂: C, 82.22; H, 11.28; N, 6.49; Found: C, 81.88; H, 10.60; N, 6.06.

3-(4-chlorophenyl)-5-p-tolyl-1H-pyrazole

White crystals, mp 236-237°C; ¹H NMR (200MHz, CD₃COCD₃) δ = 12.70 (b, 1H), 8.06-7.43 (m, 8H), 7.23 (s, 1H), 2.49 (s, 3H); ¹³C NMR (100MHz, DMSO-*d*₆) δ = 149.23, 148.54, 137.34, 132.07, 131.68, 129.43, 128.78, 127.05, 126.75, 125.03, 120.63, 99.52, 20.83; MS (m/e, %): 270 (M⁺+2, 31.66), 268 (M⁺, 100), 233 (M⁺-Cl, 5.47), 111 (C₁₀H₇, 5.70), 77 (C₆H₅, 38.64); Anal Calcd for C₁₆H₁₃ClN₂: C, 71.50; H, 4.88; N, 10.42; Found: C, 71.34; H, 4.63; N, 10.51.

3-(4-bromophenyl)-5-p-tolyl-1H-pyrazole

White crystals, mp 244-245°C; ¹H NMR (200MHz, CDCl₃) δ = 7.63-7.57 (m, 8H), 6.79 (s, 1H), 2.40 (s, 3H); ¹³C NMR (100MHz, DMSO-*d*₆) δ = 149.07,

148.14, 137.35, 132.07, 131.69, 129.44, 128.79, 127.06, 126.75, 125.04, 99.53, 20.83; MS (m/e, %): 314 (M⁺+2, 100), 312 (M⁺, 95.06), 283 (M⁺-N-NH, 2.61), 233 (M⁺-Br, 9.26); Anal Calcd for C₁₆H₁₃BrN₂: C, 61.39; H, 4.18; N, 8.94; Found: C, 61.30; H, 4.14; N, 8.93.

5-(4-chlorophenyl)-3-phenyl-1H-pyrazole

White crystals, mp 216-218°C (lit.^[17] 217°C); ¹H NMR (200MHz, CD₃COCD₃) δ = 12.65 (b, 1H), 7.97-7.36 (m, 9H), 7.19 (s, 1H); ¹³C NMR (100MHz, DMSO-*d*₆) δ = 149.12, 148.64, 132.16, 128.88, 128.83, 127.97, 126.78, 125.11, 99.90; MS (m/e, %): 256 (M⁺+2, 27.99), 254 (M⁺, 100), 225 (M⁺-N-NH, 7.43), 111 (C₁₀H₇, 4.82), 77 (C₆H₅, 43.21); Anal Calcd for C₁₅H₁₁ClN₂: C, 70.73; H, 4.35; N, 10.99; Found: C, 70.60; H, 4.244; N, 11.17.

5-(4-chlorophenyl)-3-p-tolyl-1H-pyrazole

White crystals, mp 236-237°C; ¹H NMR (200MHz, CD₃COCD₃) δ = 12.29 (s, 1H), 7.68-7.02 (m, 8H), 6.84 (s, 1H), 2.37 (s, 3H); ¹³C NMR (100MHz, DMSO-*d*₆) δ = 149.23, 148.62, 132.07, 129.44, 128.79, 126.75, 125.03, 99.53, 20.83; MS (m/e, %): 270 (M⁺+2, 35.21), 268 (M⁺, 100), 239 (M⁺-N-NH, 4.27), 111 (C₁₀H₇, 34.45), 77 (C₆H₅, 34.45); Anal Calcd for C₁₆H₁₃ClN₂: C, 71.50; H, 4.88; N, 10.42; Found: C, 71.40; H, 4.67; N, 10.58.

3,5-bis(4-chlorophenyl)-1H-pyrazole

White crystals, mp 248-249°C; ¹H NMR (200MHz, CDCl₃) δ = 7.67-7.38 (m, 8H), 6.80 (s, 1H); ¹³C NMR (100MHz, DMSO-*d*₆) δ = 149.67, 148.58, 132.34, 128.89, 126.79, 100.23; MS (m/e, %): 290 (M⁺+2, 68.23), 288 (M⁺, 100), 259 (M⁺-N-NH, 3.46), 111 (C₁₀H₇, 8.63); Anal Calcd for C₁₆H₁₃ClN₂: C, 62.30; H, 3.48; N, 9.69; Found: C, 62.47; H, 3.223; N, 9.771.

3-(4-bromophenyl)-5-(4-chlorophenyl)-1H-pyrazole

White crystals, mp 248-250°C; ¹H NMR (200MHz, CDCl₃) δ = 7.63-7.28 (m, 8H), 6.82 (s, 1H); MS (m/e, %): 334 (M⁺+2, 100), 332 (M⁺, 76.43), 305 (M⁺-N-NH, 3.55), 111 (C₁₀H₇, 8.21); Anal Calcd for C₁₆H₁₃ClN₂: C, 54.00; H, 3.02; N, 8.39; Found: C, 53.80; H, 2.807; N, 8.692.

CONCLUSIONS

In summary, a benign, simple, versatile routes to 3, 5-diarylpyrazoles in high yield have been demonstrated. In order to investigate the microwave energy transfer system both mineral supports and a polar paste system were surveyed. We have found that acetic acid is a good catalyst in a new, microwave assisted method for the products synthesis. On the other hand, the most significant result remains on using a polar paste system. The excellent product yields and simple washing with water and filtration make this methodology as an alternative platform under the umbrella of environmentally green and safe processes. In general, these approaches lead to a clean, efficient and economical technology (green chemistry); safety is largely increased, work-up is considerably simplified, cost is reduced. The extension of this type of reaction is actually under progress.

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