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ORIGINAL PAPER

Sulfamic-acid-catalyzed simple and efficient synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*] quinoline-5,10-diones under solvent-free conditions

Liqiang Wu · Suying Ma · Fulin Yan · Chunguang Yang

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Abstract An efficient synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones from the three-component condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aromatic aldehydes, and 2-hydroxy-1,4-naphthoquinone under solvent-free conditions in good to excellent yields and short reaction times using sulfamic acid as heterogeneous acid catalyst has been investigated.

Keywords Pyrazolo[3,4-*b*]quinoline · Sulfamic acid · One-pot synthesis · Solvent-free

Introduction

Pyrazolo[3,4-*b*]quinoline derivatives are used as pharmaceutical agents [1], as inhibitors of oncogenic Ras [2], and as a dopant in multilayer organic light-emitting diode (OLED) fabrication [3]. In the past several decades, three general strategies for the synthesis of pyrazolo[3,4-*b*]quinolines have been developed: (1) by the Friedlander condensation reaction of 2-aminobenzophenones and pyrazolin-5-ones [4], although availability of 2-aminobenzophenones limits the range of applicability of this reaction; (2) by cyclization of 4-arylidenepyrazolin-5-ones with anilines [5] or 5-(arylamino)pyrazoles with aromatic aldehydes [6], although the method is complicated and has a lower yield; and (3) by a three-component one-pot reaction of aromatic aldehydes, 5-amino-3-methyl-1-phenylpyrazole, and dimedone under thermal [7] or microwave conditions [8].

In recent years, the use of solid acidic catalysts has offered important advantages in organic synthesis. One of those heterogeneous catalysts is sulfamic acid (SA). It makes reaction processes convenient, more economic, and environmentally benign. Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, SA has been explored as a powerful catalyst for various organic transformations [9–12]. We report herein a highly efficient procedure for the preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones using SA as an efficient and versatile catalyst under solvent-free conditions (Scheme 1).

Results and discussion

To choose optimum conditions, first, the effect of temperature on the rate of the reaction was studied for the preparation of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo-[3,4-*b*]quinoline-5,10-dione from the three-component condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), benzaldehyde (1 mmol), and 2-hydroxy-1,4-naphthoquinone (1 mmol) under solvent-free conditions (Table 1). At 90 °C, the reaction proceeded smoothly, and almost complete conversion of product was observed. Further increase in temperature to 100 and 110 °C increased the rate of reaction. Therefore, we kept the reaction temperature at 100 °C (giving short reaction time and high yield).

Next, the study set out to determine the optimal amount of SA, so the reaction was carried out by varying the amount of catalyst (Table 1). Maximum yield was obtained with 10 mol% of catalyst. Further increase in amount of

L. Wu (✉) · S. Ma · F. Yan · C. Yang
School of Pharmacy,
Xinxiang Medical University, Xinxiang 453003, Henan,
People's Republic of China
e-mail: wliq1974@sohu.com

Scheme 1

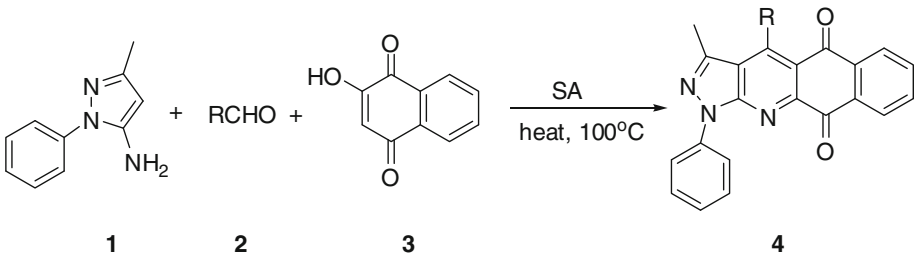


Table 1 Optimization of the one-pot synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione

Entry	SA (mol%)	Time (h)	Temp. (°C)	Yield (%)[a]
1	0	5	100	0
2	5	2	90	60
3	5	2	100	62
4	5	2	110	73
5	10	5	r.t.	<10
6	10	3	50	59
7	10	2	90	79
8	10	2	100	88
9	10	2	110	87
10	15	2	90	87
11	15	5	100	85
12	20	5	100	88

Reaction conditions: 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), benzaldehyde (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol); solvent-free

[a] Isolated yield

SA in the mentioned reaction did not have any significant effect on product yield.

The generality of this reaction was examined using several types of aldehydes. In all cases, the reactions gave the corresponding products in good to excellent yield (Table 2). This methodology offers significant improvements with regard to the scope of this transformation, simplicity of operation, and green aspects by avoiding expensive or corrosive catalysts. In addition, we noticed also that, when this reaction was carried out with aliphatic aldehydes such as butanal or pentanal, thin-layer chromatography (TLC) and ^{1}H nuclear magnetic resonance (NMR) spectra of the reaction mixture showed a combination of starting materials and numerous products, and the yield of the expected product was very poor. There were two doublets at $\delta = 8.77$–8.84 ppm for H-9 and 8.05–8.19 ppm for H-6, which probably arise from the protons *peri* to the quinone C=O. If the target compounds were another possible structure, in which the two carbonyl groups were in the *ortho*-position, they would have two doublets or dd at $\delta < 8.3$ ppm. The resonances of two nonequivalent carbonyl groups in the ^{13}C NMR spectrum of **4** appeared at $\delta = 179.8$–180.8 ppm and 179.3–180.3 ppm.

Table 2 Synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones

Entry	R	Time (h)	Product	Yield (%)[a]
1	C_6H_5	2	**4a**	88
2	4-Cl-C_6H_4	1.5	**4b**	91
3	4-MeO-C_6H_4	2	**4c**	85
4	4-Me-C_6H_4	2	**4d**	87
5	4-NO_2-C_6H_4	1.5	**4e**	93
6	4-F-C_6H_4	1.5	**4f**	90
7	3-NO_2-C_6H_4	3	**4g**	89
8	2-Cl-C_6H_4	2	**4h**	86
9	3,4-Cl_2-C_6H_3	3	**4i**	85

Reaction conditions: 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), aldehyde (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol), SA (10 mol%); 100 °C; solvent-free

[a] Isolated yield

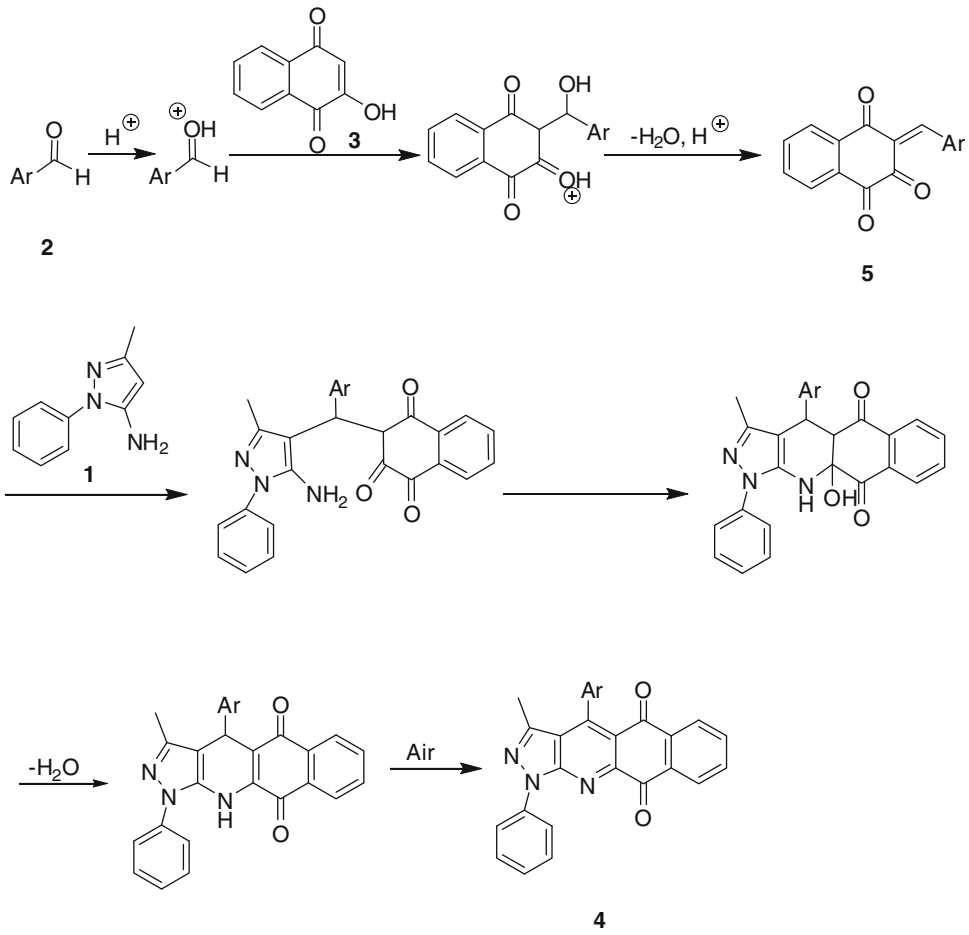
The formation of products **4a**–**4i** can be rationalized by initial formation of heterodiene **5** by standard Knoevenagel condensation of 2-hydroxynaphthalene-1,4-dione **3** and aromatic aldehyde **2** in the presence of a catalytic amount of SA. Subsequent Michael-type addition of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** to the heterodienes **5** followed by cyclization, dehydration, and air oxidation afford the corresponding products **4a**–**4i** (Scheme 2).

In summary, an efficient protocol for one-pot preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo [3,4-*b*]quinoline-5,10-diones from the three-component condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aldehyde, and 2-hydroxy-1,4-naphthoquinone using commercially available, environmentally friendly SA as catalyst was described. The reactions were carried out under thermal solvent-free conditions with short reaction time and produced the corresponding products in good to excellent yield. The one-pot nature and the use of heterogeneous solid acid as an ecofriendly catalyst make it an interesting alternative to multistep approaches.

Experimental

NMR spectra were determined on a Bruker AV-400 spectrometer at room temperature using TMS as internal

Scheme 2



standard. Elemental analyses were performed by a Vario-III elemental analyzer, and results agreed with calculated values. Melting points were determined on a XT-4 binocular microscope. Commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for the preparation of ***4***

To a mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), aldehyde (1 mmol), and 2-hydroxynaphthalene-1,4-dione (1 mmol), SA (0.1 mmol) was added. The mixture was stirred at 100 °C for an appropriate time (Table 2). After completion of the reaction (TLC), the reaction mixture was treated with 10 cm^3 water and extracted with CH_2Cl_2 (2 × 10 cm^3), filtered, and the solvent evaporated in vacuo. Products were purified by recrystallization from ethanol.

3-Methyl-1,4-diphenyl-1H-benzo[g]pyrazolo[3,4-b]-quinoline-5,10-dione (**4a**, $C_{27}H_{17}N_3O_2$)
Yellow crystals, m.p.: 266–267 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, 1H, J = 8.0 Hz), 8.31 (d, 2H, J = 7.6 Hz), 8.16 (d, 1H, J = 7.6 Hz), 7.88–7.84 (m, 1H), 7.64–7.52 (m, 6H), 7.43–7.39 (m, 1H), 7.32–7.30 (m, 2H), 1.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 179.9, 153.7, 152.2, 150.5, 146.5, 138.6, 137.3, 136.0, 135.9, 131.7, 131.3, 129.2, 129.1, 128.4, 127.2, 127.0, 126.5, 121.3, 119.8, 117.0, 14.3 ppm.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4b**, $C_{27}H_{16}ClN_3O_2$)
Yellow crystals, m.p.: 243–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, 1H, J = 8.0 Hz), 8.30 (d, 2H, J = 8.0 Hz), 8.15 (d, 1H, J = 7.6 Hz), 7.87–7.83 (m, 1H), 7.64–7.51 (m, 5H), 7.43–7.40 (m, 1H), 7.28–7.24 (m, 2H), 2.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 179.9, 153.8, 150.8, 150.5, 146.2, 138.5, 137.1, 136.0, 134.6, 134.3, 131.6, 131.4, 129.3, 129.2, 129.1, 128.7, 128.5, 127.2, 126.7, 121.4, 121.0, 119.7, 116.8, 14.5 ppm.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4c**, $C_{28}H_{19}N_3O_3$)
Yellow crystals, m.p.: 274–275 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, 1H, J = 8.0 Hz), 8.32 (d, 2H, J = 8.0 Hz), 8.16 (d, 1H, J = 8 Hz), 7.88–7.84 (m, 1H),

7.64–7.60 (m, 3H), 7.43–7.39 (m, 1H), 7.23 (d, 2H, $J = 8.4$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz), 3.93 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.8$, 180.3, 159.8, 153.8, 152.4, 150.5, 146.6, 138.6, 137.4, 136.0, 131.6, 131.3, 129.2, 129.0, 128.6, 127.7, 127.2, 126.5, 121.4, 120.2, 117.3, 113.9, 55.3, 14.6 ppm.

3-Methyl-4-(4-methylphenyl)-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4d**, $C_{28}H_{19}N_3O_2$)
Yellow crystals, m.p. 276–277 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.82$ (d, 1H, $J = 8.0$ Hz), 8.31 (d, 2H, $J = 8.0$ Hz), 8.15 (d, 1H, $J = 7.6$ Hz), 7.87–7.83 (m, 1H), 7.63–7.60 (m, 3H), 7.43–7.39 (m, 1H), 7.33 (d, 2H, $J = 7.6$ Hz), 7.18 (d, 2H, $J = 7.6$ Hz), 2.49 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.7$, 180.1, 153.7, 152.6, 150.5, 146.7, 138.6, 138.2, 137.4, 135.9, 132.8, 131.6, 131.3, 129.2, 129.1, 129.0, 127.2, 126.9, 126.5, 121.4, 120.0, 117.1, 21.5, 14.4 ppm.

3-Methyl-4-(4-nitrophenyl)-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4e**, $C_{27}H_{16}N_4O_4$)
Yellow crystals, m.p.: 326–328 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.82$ (d, 1H, $J = 8.0$ Hz), 8.42 (d, 2H, $J = 8.4$ Hz), 8.30 (d, 2H, $J = 8.0$ Hz), 8.18 (d, 1H, $J = 7.6$ Hz), 7.90–7.86 (m, 1H), 7.67–7.62 (m, 3H), 7.51 (d, 2H, $J = 8.8$ Hz), 7.46–7.42 (m, 1H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 179.8$, 179.6, 153.9, 150.5, 149.2, 147.9, 145.7, 143.1, 138.4, 136.9, 136.2, 131.7, 131.6, 129.4, 129.3, 128.2, 127.3, 126.9, 123.8, 121.5, 119.2, 116.1, 14.5 ppm.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4f**, $C_{27}H_{16}FN_3O_2$)
Yellow crystals, m.p.: 282–283 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.77$ (d, 1H, $J = 8.0$ Hz), 8.30 (d, 2H, $J = 7.6$ Hz), 8.05 (d, 1H, $J = 7.2$ Hz), 7.98–7.94 (m, 1H), 7.74–7.66 (m, 3H), 7.44–7.36 (m, 5H), 1.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.5$, 180.0, 164.1, 161.6, 153.8, 151.1, 150.2, 146.3, 138.6, 137.2, 136.0, 131.7, 131.6, 131.4, 129.3, 129.2, 129.1, 129.0, 128.9, 127.2, 126.7, 121.4, 119.9, 117.0, 115.7, 115.5, 14.4 ppm.

3-Methyl-4-(3-nitrophenyl)-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione (**4g**, $C_{27}H_{16}N_4O_4$)
Yellow crystals, m.p.: 288–289 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.83$ (d, 1H, $J = 8.0$ Hz), 8.41 (d, 1H, $J = 8.4$ Hz), 8.30 (d, 2H, $J = 8.0$ Hz), 8.24 (s, 1H), 8.18 (d, 1H, $J = 7.6$ Hz), 7.91–7.86 (m, 1H), 7.77–7.73 (m, 1H), 7.69–7.61 (m, 4H), 7.46–7.42 (m, 1H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 179.9$, 179.7, 153.9, 150.6, 148.7, 148.2, 145.6, 138.4, 137.7, 136.9, 136.2, 133.3, 131.7, 131.6, 129.6, 129.3, 129.2, 127.3, 126.9, 123.4, 122.4, 121.5, 119.4, 116.5, 14.6 ppm.

4-(2-Chlorophenyl)-3-methyl-1-phenyl-1H-benzo[g]-pyrazolo[3,4-b]quinoline-5,10-dione
(**4h**, $C_{27}H_{16}ClN_3O_2$)
Yellow crystals, m.p.: 229–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.84$ (d, 1H, $J = 8.0$ Hz), 8.33 (d, 2H, $J = 8.0$ Hz), 8.19 (d, 1H, $J = 7.6$ Hz), 7.89–7.85 (m, 1H), 7.65–7.40 (m, 7H), 7.25–7.23 (m, 1H), 2.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 179.9$, 179.3, 153.8, 150.8, 148.5, 146.2, 138.6, 137.2, 136.0, 135.1, 131.7, 131.6, 131.4, 129.9, 129.5, 129.3, 129.2, 128.3, 127.2, 127.0, 126.6, 121.4, 119.6, 116.5, 13.6 ppm.

4-(3,4-Dichlorophenyl)-3-methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-dione
(**4i**, $C_{27}H_{15}Cl_2N_3O_2$)
Yellow crystals, m.p.: 269–270 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.78$ (d, 1H, $J = 8.0$ Hz), 8.28 (d, 2H, $J = 8.0$ Hz), 8.15 (d, 1H, $J = 7.6$ Hz), 7.87–7.83 (m, 1H), 7.63–7.59 (m, 4H), 7.43–7.40 (m, 2H), 7.16 (d, 1H, $J = 8.0$ Hz), 2.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 179.9$, 179.5, 153.7, 150.4, 148.9, 145.9, 138.4, 136.9, 136.1, 135.7, 132.8, 131.5, 130.5, 129.2, 129.0, 127.2, 126.8, 126.6, 121.3, 119.4, 116.5, 14.7 ppm.

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