MgCl₂ catalyzed one-pot synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives in EG

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ABSTRACT

A green and convenient synthetic method has been described for the synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives by a one-pot, four-component reaction of aromatic aldehydes, 2-hydroxy-1,4-naphthoquinone, hydrazine derivatives and ethyl acetoacetate catalyzed by MgCl₂ in ethylene glycol. Simplicity, short reaction time, high yield and an eco-friendly catalyst are the main advantages of this method.

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In the past decades, Multi-component reactions (MCRs) have been shown to be powerful tools for the synthesis of biologically active compounds and drug candidates from simple and readily accessible starting materials.¹ They offer significant advantages over conventional synthetic strategies by shortening reaction time, reducing waste, saving energy and making full use of starting materials.²⁻⁴ Furthermore, the design of MCRs for the development of efficient chemical syntheses of complex and high added value molecules is another attractive area in chemistry.⁵⁻⁷

Naphthoquinone derivatives particularly 3-substituted-2-hydroxy-1,4-naphthoquinones are of much importance because this fragment is a key moiety in numerous biologically active compounds.⁸ For example as showed in the figure 1, atovaquone, lapachol, parvaquone and buparvaquone (Figure 1, first row) exhibit antimalarial, antibacterial, antiprotozoal, antitumor activities.⁹ Similarly, pyrazolone framework is a well-known heterocycle in many drug substances of medicinal fields. To list some pyrazolone derivatives (figure 1, second row) such as antipyrine (phenazone), 4-aminopyrine (aminophenazone), metamizol (novalgin), and 4-isopropylpyrine (propyphenazone) are all useful antipyretic and analgesic drugs.¹⁰ Pyrazolone derivatives also have ubiquitous applications in the development of acaricides, dyes, fungicides, herbicides, insecticides, inhibitors and reagents.¹¹⁻¹⁷ It is promising that the integration of these two bioactive units into a single molecule may exhibit new or improved pharmacological properties.

Considering the above points, and also in continuation of our interest on the synthesis of different kinds of heterocyclic compounds based on MCRs.¹⁸⁻²⁵ Herein we wish to report MgCl₂ as a low-toxic catalyst for one-pot synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione

derivatives via a four-component reaction of aromatic aldehydes, 2-hydroxy-1,4-naphthoquinone, hydrazine derivatives and ethyl acetoacetate in ethylene glycol (EG).

Figure 1. Typical compounds of bioactive naphthoquinones and pyrazolones

To find an appropriate reaction condition for the synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives, a one-pot four-component reaction between 4-NO₂-benzaldehyde (151.1 mg, 1.0 mmol), phenylhydrazine (108.1 mg, 1.0 mmol), ethyl acetoacetate (130.1 mg, 1.0 mmol) and 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol) was selected as a model reaction and was studied by employing a series of catalysts and solvents. **Initially, we commenced the above four-component reaction in ethanol using MgCl₂ (19mg, 20 mol%) as the catalyst and the desired compound 5a was isolated in 87% yield after 60 min of stirring** (Table 1, entry 12). Then, the reaction was carried out in EG in the presence of MgCl₂ at 100 °C, to our delight, the product was isolated in 94% yield by reacting for 20 min (Table 1, entry 9). Thus, EG was selected as the promising solvent for further screening of different catalysts. The results showed that Brønsted acid catalysts such as P-TSA, CSA, CH₃COOH exhibited a slight catalytic activity to give the product in a moderate yield (71%-80%, Table 1, entries 1–3). Better results were observed when several Lewis acid catalysts such as Cu(NO₃)₂·2H₂O, FeCl₃·6H₂O, NiCl₂·6H₂O, MgCl₂ were used, and the desired compound was obtained in 76–94% yield by reacting for a shorter time (Table 1, entries 4–6 and 9). **Other Brønsted base catalysts such as Et₃N and piperidine were investigated and did not led to any noticeable increase in the yield of the target product** (Table 1, entries 22 and 23). Control experiments showed that MgCl₂ was the most efficient catalyst for the reaction. Afterwards, the influence of different solvents was evaluated. Owing to the poor solubility of starting materials in H₂O and Glycerol, the reaction couldn't proceed smoothly (Table 1, entries 16 and 17). Other solvents like MeOH, EtOH, CH₃CN, EG, PEG-400 and PEG-600 were also examined to promote this model reaction, and EG emerged as the solvent of choice in terms of product yield and the reaction time (Table 1, entries 9, 11-15). Moreover, the loading of MgCl₂ and the proper temperature were screened for the model reaction (Table 1, entries 8-10, 18-21). Based on the above results, the optimal condition was found to be the use of catalyst MgCl₂ (19mg, 20 mol%) in EG at 100 °C.

Table1. Effect of Catalyst and Solvent on Model Reaction^a

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield ^b (%)	
1	EG	100	P-TSA(20)	120	80	
2	EG	100	CSA(20)	120	79	
3	EG	100	CH ₃ COOH(20)	120	71	
4	EG	100	Cu(NO ₃) ₂ ·2H ₂ O(20)	60	81	
5	EG	100	FeCl ₃ ·6H ₂ O(20)	60	76	
6	EG	100	NiCl ₂ ·6H ₂ O (20)	60	86	
7	EG	100	-	60	-	
8	EG	100	MgCl ₂ (10)	30	89	
9	EG	100	MgCl ₂ (20)	20	94	
10	EG	100	MgCl ₂ (30)	20	94	
11	MeOH	65	MgCl ₂ (20)	60	81	
12	EtOH	78	MgCl ₂ (20)	60	87	
13	CH ₃ CN	81	MgCl ₂ (20)	60	79	
14	PEG-400	100	MgCl ₂ (20)	90	90	
15	PEG-600	100	MgCl ₂ (20)	90	88	
16	Glycerol	100	MgCl ₂ (20)	90	trace	
17	H ₂ O	100	MgCl ₂ (20)	90	trace	
18	EG	rt	MgCl ₂ (20)	180	59	
19	EG	60	MgCl ₂ (20)	60	85	
20	EG	80	MgCl ₂ (20)	30	88	
21	EG	110	MgCl ₂ (20)	20	93	
22	EG	100	Et ₃ N	90	69	
23	EG	100	Piperidine	90	74	

^a Reactions were conducted with phenylhydrazine (108.1 mg, 1.0 mmol), ethyl acetoacetate (130.1 mg, 1.0 mmol), p-nitrobenzaldehyde (151.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), solvents (4.0 mL).

^b Isolated yields.

Under the optimal reaction conditions, the substrate scope of the reaction was investigated by using different aromatic aldehydes, β -keto esters, aryl hydrazines/hydrazine hydrate and 2-hydroxy-1,4-naphthoquinone. As shown in Table 2, the reaction with different aromatic aldehydes bearing electron-donating or electron-withdrawing substituents proceeded smoothly to afford the desired products in good to excellent yields. Meanwhile, we also found that the aromatic aldehydes

bearing electron-withdrawing substituents such as chloro, bromo, fluoro, especially nitro showed higher reactivities and gave better yields than those bearing electron-donating substituents such as methyl, methoxyl, and hydroxyl. Furthermore, the steric effects of substituents at the ortho-position of aromatic aldehydes didn't have an obvious impact on the yield of the reaction (Table 2, entries 5ae, 5ah, 5ak, and 5eb). Moreover, hydrazine derivatives and β -keto esters were applied for developing different pyrazolone rings to access the desired products in good yields (Table 2, entries 5ae-5ed). It is notable to mention here that after completion of the reaction, tautomerisation occurred in the pyrazolone rings of **5**, which may exist in two tautomeric forms. Based on the X-ray crystal structure analyses in our previous work¹⁸⁻²⁵ and Tu's work²⁶, it could be concluded that the desired products have two different structures: C=O form structure (Table 2, entries 5aa-5dc) and -OH form structure (Table 2, entries 5ea-5ed). Besides, when ethyl benzoylacetate was used as a starting material under the optimal reaction conditions, no desired product **5fa** was identified, probably because of the steric hindrance of phenyl and the low reactivity of 3-phenyl-1H-pyrazol-5(4H)-one. Some aliphatic aldehydes such as phenylacetaldehyde and butyraldehyde were also investigated for the reaction, unfortunately, no desired product was detected and most of aliphatic aldehydes remained in the reaction solution after reacting for a long time.

Table 2. Synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives^{a,b}

5ai (91%), 20min **5aj (92%), 20 min** **5ak (90%), 20 min** **5al (94%), 20 min** **5am (93%), 20 min** **5an (88%), 30 min** **5ba (85%), 50 min** **5bb (82%), 60 min** **5ca (87%), 40min** **5cb (90%), 30 min** **5cc (88%), 30 min** **5cd (84%), 60 min** **5ce (84%), 40 min** **5da (80%), 60 min** **5db (86%), 40 min** **5dc (90%), 30 min** **5ea (94%), 40 min** **5eb (89%), 40 min** **5ec (95%), 20 min** **5ed (90%), 40 min** **5fa (not obtained), 3 h** **5ga (not obtained), 3 h**

^a Reactions were conducted with aryl hydrazines/hydrazine hydrate (1.0 mmol), β -keto esters (1.0 mmol), aromatic aldehydes (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), MgCl_2 (20 mol%), EG (4.0 mL).

^b Isolated yields.

In another investigation, we carried out the reaction in many other conditions for the synthesis of pyran derivatives **6** (scheme 1). Unfortunately, when the same reaction was carried out in different solvents at higher temperatures for longer

reaction times, no pyran compounds **6** were formed and instead gave compounds **5** in good yields. In control experiments, we replaced aromatic aldehydes with isatin and acenaphthenequinone under the same reaction conditions. Surprisingly, the reaction produced the pyran derivatives **6b** and **6c** in high yields (scheme 1). This anomaly may result from the more stability of compounds **5** in enol form and the hydrogen bond action. Finally, it is worth mentioning that these two kinds of reactions all displayed good results when the EG/MgCl₂ system was used.

Scheme 1. Synthesis of **5ec**, **6b** and **6c** catalyzed by MgCl_2 in EG

The plausible mechanism that could be accounted for this four-component reaction is depicted in Scheme 2. Firstly, aryl hydrazine/hydrazine hydrate **1** is reacted with β -keto esters **2** to generate the pyrazolone ring **7**, which is then isomerized to intermediate **8**. Additionally, Lewis acidic virtue of MgCl_2 causes to activation of aldehyde carbonyl group to attack of 2-hydroxy-1,4-naphthoquinone **3**. Nucleophilic attack of 2-hydroxy-1,4-naphthoquinone **3** to activated aldehyde **4** leads to intermediate **9** with C–C bond formation and unsaturated Knoevenagel product **11** is formed with the elimination of MgCl_2 and H_2O . Subsequently, Michael addition of intermediate **8** to unsaturated Knoevenagel product **11** occurs to provide intermediate **12**, which undergoes tautomeric proton shift to generate the target product **5**.

Scheme 2. The plausible reaction mechanism.

In conclusion, we have developed an efficient and practical procedure for the synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives via a one-pot, four-component reaction of aromatic aldehydes, β -keto esters, aryl hydrazines/hydrazine hydrate and 2-hydroxy-1,4-naphthoquinone catalyzed by MgCl_2 in EG at 100 °C. The attractive features of this protocol are simple work up procedure, short reaction time, high yield and an eco-friendly catalyst, which make it a useful and attractive strategy in synthetic organic chemistry. Further studies on the application of this procedure are ongoing in our laboratory.

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Supporting Information

Spectroscopic data, copies of ^1H NMR, ^{13}C NMR, HRMS (ESI) and FT-IR spectra of all new compounds. This material is available free of charge via the Internet at <https://www.elsevier.com>

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- 27 **General procedure for the synthesis of**

2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives (5aa-5ed). To a mixture of β -keto esters (1.0 mmol) and aryl hydrazines/ hydrazine hydrate (1.0 mmol) in EG (4.0 ml) was added aldehydes (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), and MgCl_2 (0.2 mmol). The mixture was stirred at 100°C and monitored by TLC. Upon completion (20–60 min) of the reaction, the reaction mixture was cooled to room temperature and 4 mL water was added to it. Then the precipitated products were filtered and washed with water (5 ml $\times$ 3) and cold ethanol (4 ml $\times$ 2). The isolated product was recrystallized from ethanol to get the pure products **5**.

General procedure for the synthesis of pyran derivatives (6b and 6c). To a mixture of β -keto esters (1.0 mmol) and aryl hydrazines/ hydrazine hydrate (1.0 mmol) in EG (4.0 ml) was added isatin or acenaphthenequinone (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), and MgCl_2 (0.2 mmol). The mixture was stirred at 100°C and monitored by TLC. Upon completion (2–3h) of the reaction, the reaction mixture was cooled to room temperature and 4 mL water was added to it. Then the precipitated products were filtered and washed with hot water (5 ml $\times$ 3) and cold ethanol (3 ml $\times$ 2) to afford the pure products **6b** and **6c** without further purification.

Data for selected products:

2-hydroxy-3-((3-hydroxy-5-propyl-1H-pyrazol-4-yl)(4-nitrophenyl)methyl)naphthalene-1,4-dione(5ec). Yellow-orange powder; m.p. 242–244°C; IR (KBr, ν , cm^{-1}): 3080, 2962, 2872, 1676, 1591, 1560, 1510, 1350, 1277, 1247, 1112, 1056, 954, 908, 844, 732, 700, 664. ^1H NMR (500 MHz, DMSO) δ 16.09 (s, 1H), 13.17 (s, 2H), 8.13 – 8.08 (m, 2H), 8.02 (dd, J = 7.6, 0.7 Hz, 1H), 7.92 (dd, J = 7.6, 1.0 Hz, 1H), 7.80 (td, J = 7.5, 1.3 Hz, 1H), 7.73 (td, J = 7.5, 1.2 Hz, 1H), 7.43 – 7.37 (m, 2H), 5.89 (s, 1H), 2.73 (dt, J = 14.8, 7.5 Hz, 1H), 2.58 (dt, J = 14.7, 7.5 Hz, 1H), 1.64 – 1.46 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 183.36, 182.61, 163.49, 160.76, 149.78, 147.34, 145.76, 134.08, 132.68, 132.50, 130.97, 128.22, 125.91, 125.50, 123.78, 123.23, 102.44, 32.12, 26.28, 21.62, 13.53. HRMS (ESI) Calcd. For $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 434.1347. Found: 434.1338.

8-propyl-5H-spiro[benzo[7,8]chromeno[2,3-c]pyrazole-7,3'-indoline]-2',5,6(9H)-trione(6b). Red powder; m.p. >320°C; IR (KBr, ν , cm^{-1}): 3323, 3078, 2954, 2870, 1709, 1660, 1609, 1568, 1471, 1348, 1292, 1232, 1152, 1090, 1032, 956, 939, 779, 756, 709, 673, 634. ^1H NMR (500 MHz, DMSO) δ 12.59 (s, 1H), 10.79 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 8.02 (d, J = 7.1 Hz, 1H), 7.98 – 7.90 (m, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.25 – 7.15 (m, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 2.16 – 1.86 (m, 2H), 1.21 – 0.84 (m, 2H), 0.57 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 178.63, 178.11, 177.77, 160.32, 154.95, 142.42, 141.05, 136.34, 134.87, 132.76, 130.74, 130.46, 129.29, 129.09, 125.50, 124.38, 122.92, 113.68, 110.12, 96.99, 47.92, 26.41, 21.68, 13.99. HRMS (ESI) Calcd. For $\text{C}_{24}\text{H}_{18}\text{N}_3\text{O}_4$ ($[\text{M}+\text{H}]^+$): 412.1292. Found: 412.1303.

8'-propyl-2H,5'H-spiro[acenaphthylene-1,7'-benzo[7,8]chromeno[2,3-c]pyrazole]-2,5',6'(9'H)-trione(6c). Red powder; m.p. >320°C; IR (KBr, ν , cm^{-1}): 3361, 3050, 2962, 2931, 2868, 1724, 1652, 1602, 1566, 1473, 1344, 1290, 1240, 1172, 1089, 1039, 997, 981, 956, 837, 783, 698, 627. ^1H NMR (500 MHz, DMSO) δ 12.55 (s, 1H), 8.38 (d, J = 7.7 Hz, 1H), 8.20 (d, J = 7.3 Hz, 1H), 8.09 (d, J = 6.4 Hz, 1H), 7.97 (dd, J = 21.9, 7.8 Hz, 4H), 7.77 (d, J = 6.9 Hz, 1H), 7.63 (t, J = 7.0 Hz, 1H), 7.41 (d, J = 6.4 Hz, 1H), 1.51 – 1.26 (m, 2H), 0.35–0.75 (m, 2H), 0.10 (t, J = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 202.31, 177.57, 177.19, 159.76, 154.33, 143.09, 140.53, 140.03, 135.51, 132.49, 131.98, 131.86, 130.28, 130.22, 129.85, 129.09, 128.71, 128.48, 124.80, 124.58, 121.94, 120.86, 114.44, 97.79, 52.04, 26.16, 21.16, 13.02. HRMS (ESI) Calcd. For $\text{C}_{28}\text{H}_{19}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$): 447.1339. Found: 447.1344.

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