

Article

Microwave-Assisted One-Pot Synthesis of Pyrazolone Derivatives under Solvent-Free Conditions

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Received: 23 April 2010; in revised form: 10 May 2010 / Accepted: 13 May 2010 /

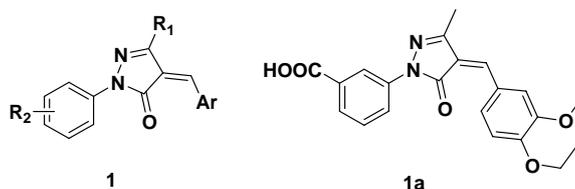
Published: 17 May 2010

Abstract: An efficient one-pot method to generate structurally diverse and medicinally interesting pyrazolone derivatives in good to excellent yields of 51–98% under microwave irradiation and solvent-free conditions has been developed.

Keywords: microwave-assisted reactions; one-pot; pyrazolones

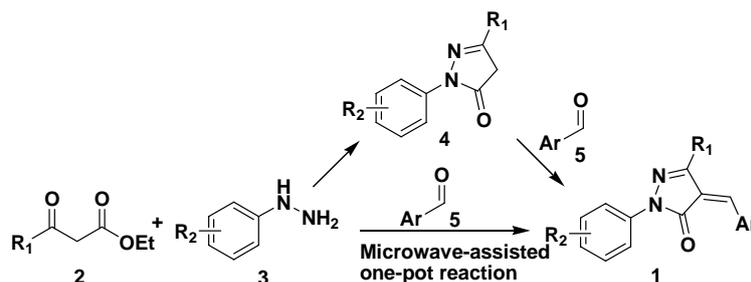
1. Introduction

Pyrazolone derivatives are an important class of heterocyclic compounds that occur in many drugs and synthetic products [1]. These compounds exhibit remarkable antitubercular [2,3], antifungal [4,5], antibacterial [6], anti-inflammatory [7], and antitumor activities [8]. In our effort to identify new farnesoid X receptor (FXR) ligands [9], we recently found by virtual screening that a 4-arylidene-pyrazolone derivative **1a** (Figure 1) was a FXR antagonist (unpublished data). Consequently, to explore the structure activity relationships (SAR) for this family of compounds, a facile and practical approach for synthesizing 4-arylidene-pyrazolone-containing derivatives **1** (Figure 1) became desirable.

Figure 1. The structures of 4-arylidene-pyrazolone derivatives **1** and FXR antagonist **1a**.

Generally, 4-arylidene-pyrazolone derivatives **1** are synthesized using as starting materials substituted aldehydes **5** [10–12] (or their their acetal [13,14] or imine [15,16] precursors) and 2-pyrazolin-5-ones **4**, the latter generally being obtained by the Knorr condensation [17,18] of β -ketoesters **2** with substituted hydrazines **3** (Scheme 1). It is obvious that all described methods involve multiple step reactions and most of them produce equimolar amounts of unwanted by-products. In this respect, the development of a one-pot reaction using readily available chemicals would be of considerable significance due to its synthetic efficiency and atom economy.

Scheme 1. The synthetic routes to 4-arylidene-pyrazolone derivatives **1** by classical two step or the proposed one-pot method.



Microwave-assisted organic reactions have been applied to a wide range of reaction types [19–25], especially cycloaddition reactions. Microwaves accelerate a variety of synthetic transformations providing time- and energy-saving protocols [19–25]. Recently, Botta *et al.* [26]. reported a microwave-assisted three-component Knoevenagel/hetero Diels–Alder reaction, which suggested that 2-pyrazolin-5-ones **4** might react well with aldehydes **5** under microwave irradiation conditions. Inspired by this reaction, we envisioned that a new three-component (compounds **2**, **3**, and **5**) one-pot reaction might take place using a microwave-assisted approach and would directly create the target 4-arylidene-pyrazolone scaffolds **1** (Scheme 1).

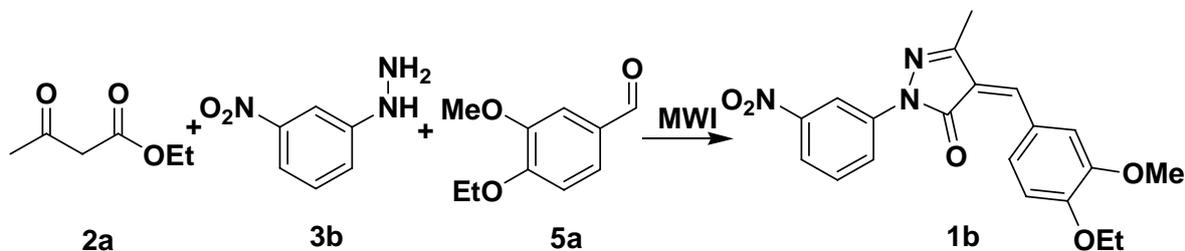
2. Results and Discussion

2.1. Optimization of the reaction conditions

Initially we selected ethyl acetoacetate (**2a**), 3-nitrophenylhydrazine (**3b**) and 3-methoxy-4-ethoxy-benzaldehyde (**5a**) as the model substrates for the optimization of the reaction conditions, which included microwave oven power, time of irradiation, solid supports and reactant ratios. The results are summarized in Tables 1-2. The preliminary investigations revealed that the one-pot reaction occurred,

as designed. Nevertheless, the reaction efficiency was highly microwave oven power dependent (entries 1-3, Table 1), with a good yield being achieved at 420 W. We then compared the synthesis of **1b** with irradiation times of 5 min, 10 min, and 15 min at 420 W, and the corresponding yields were 54%, 71%, and 62%, respectively (entries 2 and 4,5, Table 1).

Table 1. Optimization of the power of microwave oven and time of irradiation.^a



Entry	Power (W)	Time (min)	Yield (%) ^b
1	280	5	20
2	420	5	67
3	560	5	54
4	420	10	71
5	420	15	62

^a the reaction was carried out with **2a**, **3b** and **5a** in equimolar ratio (0.3 mmol); for the detailed reaction conditions see the Experimental section; ^b Isolated yields.

Table 2. Optimization of the reactant's equivalence ratio and solid support.^a

Entry	Solid support	Reagent Ratio			Yield (%) ^b
		2a	3b	5a	
1	-	1	1.2	1	60
2	-	1.2	1	1	78
3	-	1	1	1.2	63
4	-	1.5	1	1	83
5	-	2	1	1	73
6	-	2.5	1	1	79
7	-	3	1	1	81
8	SiO ₂	1.5	1	1	81
9	Al ₂ O ₃	1.5	1	1	80

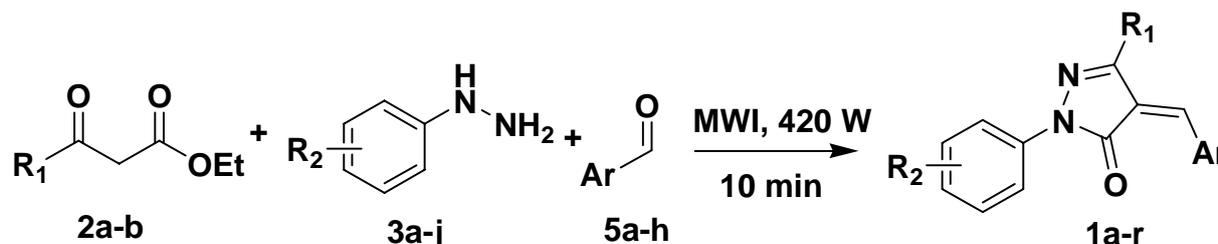
^a The reaction was carried out under microwave radiation 420 W for 10 min; for detailed reaction conditions see the Experimental section; ^b Isolated yields.

Encouraged by the promising results, we further optimized the reactant ratio (entries 1–7, Table 2) and solid support (entries 8,9, Table 2). The optimum results were obtained when the reactants were mixed in a ratio of **2a/3b/5a** = 1.5/1/1 without solid support and irradiated at 420 W for 10 min (entry 4, Table 2). Solid supports such as aluminium oxides and silica gel have been widely used in microwave-assisted organic synthesis to enhance substrates absorption of microwave energy. However, solid supports appeared to offer no advantages in our one-pot reaction (entries 4, and 8,9, Table 2).

2.2. Scope of microwave-assisted one-pot synthesis of 4-arylidene-pyrazolone derivatives

Having established the optimal reaction conditions, we subjected a series of β -ketoesters, hydrazines, and aldehydes to them to explore the generality and scope of the one-pot process. As shown in Table 3, we were pleased to find that this method was applicable to a broad range substrate of substituted β -ketoester (**2a-b**), hydrazine (**3a-j**), and aldehyde (**5a-h**) substrates.

Table 3. Scope of microwave-assisted one-pot synthesis of 4-arylidene-pyrazolone derivatives.^a



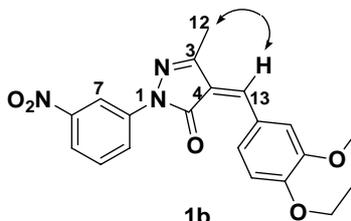
Compd.	R ₁	R ₂	Ar	Yield (%) ^b
1a	Me, 2a	3-CO ₂ H, 3a	3-MeO-4-EtO-Ph, 5a	98
1b	Me, 2a	3-NO ₂ , 3b	3-MeO-4-EtO-Ph, 5a	83
1c	Me, 2a	4-NO ₂ , 3c	3-MeO-4-EtO-Ph, 5a	78
1d	Me, 2a	4-CF ₃ , 3d	3-MeO-4-EtO-Ph, 5a	53
1e	Me, 2a	3-CF ₃ , 3e	3-MeO-4-EtO-Ph, 5a	67 ^c
1f	Me, 2a	3,5-di-CF ₃ , 3f	3-MeO-4-EtO-Ph, 5a	54 ^c
1g	Me, 2a	2-F, 3g	3-MeO-4-EtO-Ph, 5a	51
1h	Me, 2a	3,4-di-Cl, 3h	3-MeO-4-EtO-Ph, 5a	86
1i	Me, 2a	3,5-di-Cl, 3i	3-MeO-4-EtO-Ph, 5a	73 ^c
1j	Me, 2a	3-CO ₂ H, 3a	3-MeO-4-OH-Ph, 5b	68
1k	Me, 2a	3-CO ₂ H, 3a	3,4-di-OH-Ph, 5c	73
1l	Me, 2a	3-NO ₂ , 3b	5-Me-thiophen-2-yl, 5d	53
1m	Me, 2a	H, 3j	3-MeO-4-EtO-Ph, 5a	63
1n	Me, 2a	H, 3j	4-Br-Ph, 5e	53 ^c
1o	Ph, 2b	3-NO ₂ , 3b	3-MeO-4-OH-Ph, 5c	61
1p	Me, 2a	3-CO ₂ H, 3a	3-MeO-4-PhCH ₂ O-Ph, 5f	84
1q	Me, 2a	3-CO ₂ H, 3a	3-MeO-4-Me(CH ₂) ₄ O-Ph, 5g	83
1r	Me, 2a	3-CO ₂ H, 3a	3-MeO-4-Me ₂ CHO-Ph, 5h	76

^a Unless stated otherwise, the reaction was carried out with **2** (0.45 mmol), **3** (0.3 mmol) and **5** (0.3 mmol) under microwave radiation 420 W for 10 min; for the detailed reaction conditions see the Experimental section; ^b Isolated yields; ^c These reactions were carried out with **2** (0.36 mmol), **3** (0.3 mmol) and **5** (0.3 mmol).

The target products **1a-r** were prepared in good to excellent yields (51–98%). A variety of substituents on the aryl ring including halogens, -CO₂H, -NO₂, -CF₃, alkoxy, *etc.* were well tolerated. These outcomes imply that electronic features have a marginal effect on the process. Examination of the results also revealed that the steric effects also play a minimal role in governing the reaction efficiency, as all *para*- (such as compound **1c**), *meta*- (such as compound **1e**), and *ortho*- (such as compound **1g**) substituted substrates were smoothly transformed into the desired products. Heterocycles (compound **1l**) could efficiently participate in the one-pot reaction as well. Finally, it is noteworthy that the process features simple operation and purification, and all target products could be directly obtained by simple suction filtration and washing with ethyl acetate.

With regard to the stereochemistry of the 4-arylidene-pyrazolone products **1a-r**, they were all exclusively assigned the *Z*-configuration based on NOE spectroscopy of compound **1b**. NOE was observed between H-13 (δ 7.37) and H-12 (δ 2.38), suggesting a *Z* configuration at $\Delta^{[4,13]}$ (Figure 2).

Figure 2. NOE correlation (double-headed arrows) established the stereochemistry of the double bond in **1b**.



3. Experimental

3.1. General

The reagents were purchased from Shanghai Chemical Reagent Company, Lancaster, and Acros, and used without further purification. Yields were not optimized. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX-400 NMR instrument (^1H at 400 MHz and ^{13}C at 100 MHz, respectively). Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) used as internal standard. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained by electron ionization (EI) on a Finnigan MAT-95 instrument. Microwave experiments were carried out in a domestic microwave oven (Midea MM721AAU-PW).

3.2. General Procedure for the Preparation of **1a-r**: Preparation of **1b**

(Z)-4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-1-(3-nitrophenyl)-pyrazolone (**1b**). A one-neck 50-mL flask containing ethyl acetoacetate (**2a**, 0.45 mmol), 3-nitrophenylhydrazine (**3b**, 0.3 mmol) and 3-methoxy-4-ethoxy-benzaldehyde (**5a**, 0.3 mmol) was placed in a domestic microwave oven and irradiated at a power of 420 W for 10 min. The solid obtained after cooling was triturated with ethyl acetate and collected by suction filtration, to afford product **1b** (95 mg, yield 83%) as an orange solid. m.p. 212–213 °C. $^1\text{H-NMR}$ (CDCl_3): δ 1.55 (t, 3H), 2.38 (s, 3H), 4.07 (s, 3H), 4.27 (q, 2H), 6.98 (d, 1H), 7.37 (s, 1H), 7.59 (t, 1H), 7.75 (d, 1H), 8.03 (d, 1H), 8.47 (d, 1H), 8.93 (d, 2H); $^{13}\text{C-NMR}$ (CDCl_3): δ 162.7, 153.6, 152.1, 149.0, 148.6, 148.3, 139.6, 130.9, 129.6, 126.5, 124.0, 123.9, 118.8, 115.8, 113.5, 111.4, 64.7, 56.4, 14.6, 13.5; EI-MS m/z 381 (M^+ , 100%); HRMS (EI) m/z calcd. $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5$ (M^+) 381.1325, found 381.1321.

(Z)-3-(4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (**1a**). Solid. m.p. 276–278 °C. $^1\text{H-NMR}$ (DMSO): δ 1.38 (t, 3H), 2.34 (s, 3H), 3.88 (s, 3H), 4.17 (q, 2H), 7.16 (d, 1H), 7.56 (t, 1H), 7.77 (s, 2H), 8.12 (d, 1H), 8.21 (d, 1H), 8.51 (s, 1H), 8.75 (s, 1H),

13.05 (s, 1H); EI-MS m/z 380 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{21}H_{20}N_2O_5$ (M^+) 380.1372, found 380.1371.

(*Z*)-4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-1-(4-nitrophenyl)-1*H*-pyrazol-5(4*H*)-one (**1c**). Solid. m.p. 213–215 °C. 1H -NMR ($CDCl_3$): δ 1.55 (t, 3H), 2.38 (s, 3H), 4.06 (s, 3H), 4.25 (q, 2H), 6.97 (d, 1H), 7.37 (s, 1H), 7.73 (d, 1H), 8.29 (s, 4H), 8.90 (s, 1H); EI-MS m/z 381 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{20}H_{19}N_3O_5$ (M^+) 381.1325, found 381.1323.

(*Z*)-4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5(4*H*)-one (**1d**). Solid. m.p. 144–147 °C. 1H -NMR ($CDCl_3$): δ 1.54 (t, 3H), 2.37 (s, 3H), 4.05 (s, 3H), 4.25 (q, 2H), 6.96 (d, 1H), 7.35 (s, 1H), 7.66 (d, 2H), 7.72 (d, 1H), 8.18 (d, 2H), 8.93 (s, 1H); EI-MS m/z 404 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{21}H_{19}F_3N_2O_3$ (M^+) 404.1348, found 404.1349.

(*Z*)-4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5(4*H*)-one (**1e**). Solid. m.p. 147–151 °C. 1H -NMR ($CDCl_3$): δ 1.54 (t, 3H), 2.37 (s, 3H), 4.06 (s, 3H), 4.24 (q, 2H), 6.97 (d, 1H), 7.35 (s, 1H), 7.42 (d, 1H), 7.53 (t, 1H), 7.75 (d, 1H), 8.28 (d, 1H), 8.31 (s, 1H), 8.91 (s, 1H); EI-MS m/z 404 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{21}H_{19}F_3N_2O_3$ (M^+) 404.1348, found 404.1349.

(*Z*)-1-(3,5-bis(Trifluoromethyl)phenyl)-4-(4-ethoxy-3-methoxybenzylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**1f**). Solid. m.p. 198–200 °C. 1H -NMR ($CDCl_3$): δ 1.54 (t, 3H), 2.38 (s, 3H), 4.07 (s, 3H), 4.25 (q, 2H), 6.98 (d, 1H), 7.37 (s, 1H), 7.65 (s, 1H), 7.77 (d, 1H), 8.61 (s, 2H), 8.84 (s, 1H); EI-MS m/z 472 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{22}H_{18}F_6N_2O_3$ (M^+) 472.1222, found 472.1223.

(*Z*)-4-(4-Ethoxy-3-methoxybenzylidene)-1-(2-fluorophenyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**1g**). Solid. m.p. 153–155 °C. 1H -NMR ($CDCl_3$): δ 1.52 (t, 3H), 2.34 (s, 3H), 4.00 (s, 3H), 4.22 (q, 2H), 6.93 (d, 1H), 7.22 (q, 2H), 7.32 (t, 1H), 7.36 (s, 1H), 7.52 (t, 1H), 7.67 (d, 1H); EI-MS m/z 354 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{20}H_{19}FN_2O_3$ (M^+) 354.1380, found 354.1377.

(*Z*)-1-(3,4-Dichlorophenyl)-4-(4-ethoxy-3-methoxybenzylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**1h**). Solid. m.p. 164–166 °C. 1H -NMR ($CDCl_3$): δ 1.53 (t, 3H), 2.34 (s, 3H), 4.05 (s, 3H), 4.23 (q, 2H), 6.95 (d, 1H), 7.32 (s, 1H), 7.44 (s, 1H), 7.71 (d, 1H), 7.94 (d, 1H), 8.21 (s, 1H), 8.90 (s, 1H); EI-MS m/z 404 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{22}H_{18}F_6N_2O_3$ (M^+) 404.0694, found 404.0695.

(*Z*)-1-(3,5-Dichlorophenyl)-4-(4-ethoxy-3-methoxybenzylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**1i**). Solid. m.p. 182–185 °C. 1H -NMR ($CDCl_3$): δ 1.54 (t, 3H), 2.35 (s, 3H), 4.06 (s, 3H), 4.23 (q, 2H), 6.96 (d, 1H), 7.15 (s, 1H), 7.33 (s, 1H), 7.72 (d, 1H), 8.04 (s, 2H), 8.89 (s, 1H); EI-MS m/z 404 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{22}H_{18}F_6N_2O_3$ (M^+) 404.0694, found 404.0697.

(*Z*)-3-(4-(4-Hydroxy-3-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzoic acid (**1j**). Solid. m.p. 255–257 °C. 1H -NMR (DMSO): δ 2.33 (s, 3H), 3.90 (s, 3H), 6.96 (d, 1H), 7.56 (t, 1H), 7.70 (s, 1H), 7.75 (d, 1H), 8.04 (d, 1H), 8.21 (d, 1H), 8.53 (s, 1H), 8.76 (s, 1H); EI-MS m/z 352 (M^+ , 100%); HRMS (EI) m/z calcd. $C_{19}H_{16}N_2O_5$ (M^+) 352.1059, found 352.1057.

(*Z*)-3-(4-(3,4-Dihydroxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl) benzoic acid (**1k**). Solid. m.p. 278–280 °C. ¹H-NMR (DMSO): δ 2.34 (s, 3H), 6.93 (d, 1H), 7.57 (t, 1H), 7.65 (s, 1H), 7.76 (d, 1H), 7.92 (d, 1H), 8.18 (d, 1H), 8.52 (s, 1H), 8.63 (s, 1H), 10.45(s,1H); EI-MS m/z 338 (M⁺, 100%); HRMS (EI) m/z calcd. C₁₉H₁₆N₂O₅ (M⁺) 338.0903, found 338.0782.

(*Z*)-3-Methyl-4-((5-methylthiophen-2-yl)methylene)-1-(3-nitrophenyl)-1*H*-pyrazol-5(4*H*)-one (**1l**). Solid. m.p. 199–201 °C. ¹H-NMR (CDCl₃): δ 2.39 (s, 1H), 2.67 (s, 3H), 7.00 (s, 1H), 7.58 (t, 2H), 7.85 (s, 1H), 8.02 (d, 1H), 8.53 (d, 1H), 8.92 (s, 1H); EI-MS m/z 327 (M⁺, 100%); HRMS (EI) m/z calcd. C₁₆H₁₃N₃O₃S (M⁺) 327.0678, found 327.0675.

(*Z*)-4-(4-Ethoxy-3-methoxybenzylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1m**). Solid. m.p. 134–139 °C. ¹H-NMR (CDCl₃): δ 1.54 (t,3H), 2.36 (s, 3H), 4.05 (s, 3H), 4.23 (q, 2H), 6.95 (d, 1H), 7.19 (t, 1H), 7.32 (s, 1H), 7.42 (t, 2H), 7.72 (d, 1H), 7.97 (d, 2H), 8.98 (s, 1H); EI-MS m/z 336 (M⁺, 100%); HRMS (EI) m/z calcd. C₂₀H₂₀N₂O₃ (M⁺) 336.1474, found 336.1475.

(*Z*)-4-(4-Bromobenzylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1n**). Solid. m.p. 117–120 °C. ¹H-NMR (CDCl₃): δ 2.36 (s, 3H), 7.21 (t, 1H), 7.32 (s, 1H), 7.43 (t, 2H), 7.65 (d, 2H), 7.95 (d, 2H), 8.39 (d, 2H); EI-MS m/z 340 (M⁺, 100%); HRMS (EI) m/z calcd. C₁₇H₁₃BrN₂O (M⁺) 340.0211, found 340.0212.

(*Z*)-4-(4-Hydroxy-3-methoxybenzylidene)-1-(3-nitrophenyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (**1o**). Solid. m.p. 199–202 °C. ¹H-NMR (CDCl₃): δ 4.14 (s, 3H), 6.38 (s, 1H), 7.03 (d, 1H), 7.53 (d, 1H), 7.56 (m, 4H), 7.69 (d, 1H), 7.71 (d, 1H), 8.07 (d, 1H), 8.54 (d, 1H), 9.06 (s, 1H), 9.15 (s, 1H); EI-MS m/z 415 (M⁺, 100%); HRMS (EI) m/z calcd. C₂₃H₁₇N₃O₅ (M⁺) 415.1168, found 415.1159.

(*Z*)-3-(4-(4-(Benzyloxy)-3-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzoic acid (**1p**). Solid. m.p. 249–252 °C. ¹H-NMR (DMSO): δ 2.35 (s, 3H), 3.89 (s, 3H), 5.26 (s,2H), 7.28–7.50 (m, 7H), 7.57 (t, 1H), 7.77 (d, 2H), 8.14 (d, 1H), 8.22 (d, 1H), 8.52 (s, 1H), 8.77 (s, 1H); EI-MS m/z 442 (M⁺, 100%); HRMS (EI) m/z calcd C₂₆H₂₂N₂O₅ (M⁺) 442.1529, found 442.1530.

(*Z*)-3-(4-(3-Methoxy-4-(pentyloxy)benzylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzoic acid (**1q**). Solid. m.p. 224–226 °C. ¹H-NMR (DMSO): δ 0.91 (t, 3H), 1.32–1.43 (m, 4H), 1.77 (m, 2H), 2.35 (s, 3H), 3.88 (s, 3H), 4.11 (t, 2H), 7.18 (d,1H), 7.57 (t, 1H), 7.77 (d, 2H), 8.13 (d, 1H), 8.22 (d, 1H), 8.52 (s, 1H), 8.77 (s, 1H); EI-MS m/z 422 (M⁺, 100%); HRMS (EI) m/z calcd. C₂₄H₂₆N₂O₅ (M⁺) 422.1842, found 422.1840.

(*Z*)-3-(4-(4-Isopropoxy-3-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzoic acid (**1r**). Solid. m.p. 206–208 °C. ¹H-NMR (DMSO): δ 1.33 (s, 6H), 2.36 (s, 3H), 3.87 (s, 3H), 4.83 (m, 1H), 7.21 (d, 1H), 7.57 (t,1H), 7.76 (d, 1H), 7.79 (s, 1H), 8.15 (d, 1H), 8.22 (d, 1H), 8.53 (s, 1H), 8.75 (s, 1H); EI-MS m/z 394 (M⁺, 100%); HRMS (EI) m/z calcd. C₂₄H₂₆N₂O₅ (M⁺) 394.1529, found 394.1528.

4. Conclusions

We have developed a simple, rapid, and efficient one-pot protocol for the preparation of the 4-arylidene-pyrazolone derivatives by a solvent-free, microwave-assisted reaction. Furthermore, the procedure used commercially available reagents, giving the desired compounds in good to excellent yields (51–98%). The versatility of this methodology makes it suitable for library synthesis in drug discovery efforts.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (Grants 90813005, 20902022, 30801415 and 30890044), the Open Project Program of State Key Laboratory of Drug Research (Grant SIMM0901KF-03) and Shanghai Rising-Star Program (Grant 09QA1406800).

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Sample Availability: Samples of the compounds reported in this paper are available from the authors.