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Atom- and step-economic synthesis of biaryl-substituted furocoumarins, furoquinolones and furopyrimidines by multicomponent reactions and one-pot synthesis

Abstract: Atom-efficient multicomponent reactions (MCR) and step-efficient one-pot synthesis are developed for the synthesis of biaryl-substituted furocoumarins, furoquinolones, and furopyrimidines. Furocoumarin and furoquinolone derivatives are synthesized by a three-component reaction, followed by the Suzuki coupling reaction. Furopyrimidine derivatives are prepared by the Suzuki coupling and then the three-component reaction. The bromobenzaldehydes are the key bifunctional molecules for the multicomponent and Suzuki coupling reactions.

Keywords: atom economy; furocoumarin; furopyrimidine; furoquinolone; multicomponent reaction; one-pot synthesis; step economy.

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1 Introduction

Synthetic efficiency is important for atom economy and reducing chemical waste. A multicomponent reaction (MCR) is highly atom economic, which generates multiple chemical bonds in a simple operation. All of the reagents are introduced spontaneously and no distinguishable intermediate can be isolated from the MCR. One-pot synthesis is step economic, because no intermediates need to be separated from multi-step reactions. Introduced in this paper, is the combination of MCR and one-pot synthesis for the preparation of biaryl-substituted heterocyclic compounds, including furocoumarins, furoquinolones, and furopyrimidines.

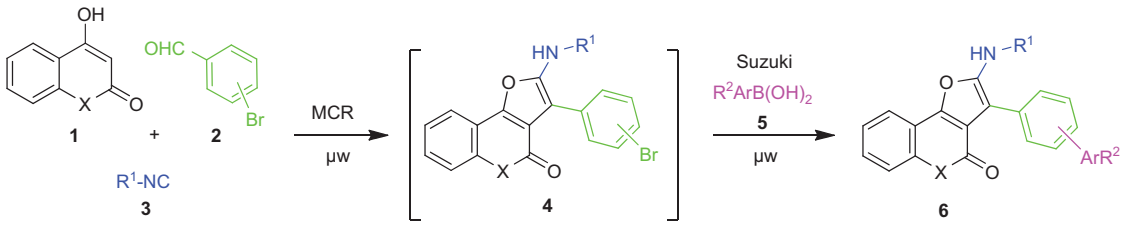
Furocoumarins, furoquinolones, and furopyrimidines are furan-fused coumarin, quinolone, and pyrimidine systems. Conjugated furans have unique photophysical and electrochemical properties and have been investigated as fluorescent dyes, photosensitizers, organic light emitting diodes, two-photon absorption materials, second and higher order nonlinear optics, and supramolecular materials [1–4]. Coumarin, quinolone, and pyrimidine are privileged-ring systems found in numerous natural products and synthetic compounds which have a wide range of biological activities and developed as antifungal, antibacterial, antiviral, antimicrobial, and anticonvulsant agents [5–13]. The combination of furan with coumarin, quinolone, or pyrimidine could result in unique heterocyclic molecules for photophysical, photochemical and biological studies.

We introduce in this paper a new strategy for atom- and step-economic synthesis of furocoumarin, furoquinolone, and furopyrimidine derivatives. The synthesis of furocoumarin and furoquinolone derivatives **6** was accomplished by a three-component reaction, followed by the one-pot Suzuki coupling reaction (Scheme 1). The synthesis of furopyrimidine derivatives **9** was accomplished by the Suzuki coupling of bromobenzaldehydes, followed by the three-component reaction (Scheme 2). All the reactions shown in Schemes 1 and 2 were promoted by microwave (μw) heating to reduce reaction time and increase synthetic efficiency.

2 Experimental section

2.1 General information

All chemicals and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian NMR spectrometer. LC-MS were performed on an Agilent 2100 system (Santa Clara, CA, USA) with a C_{18} column (5.0 μm, 6.0×50 mm). The mobile phases were MeOH and water, both containing 0.05% trifluoroacetic acid. A linear gradient was started from



Scheme 1 One-pot synthesis of furocoumarins (X=O) and furoquinolones (X=NMe).

75:25 MeOH/H_2O to 100% MeOH in 5 min at a flow rate of 0.7 ml/min. The chromatograms were recorded at UV 210 nm, 254 nm, and 365 nm. Low resolution mass spectra were recorded in atmospheric pressure chemical ionization (APCI). High resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Flash chromatography separations were performed on YAMAZEN AI-580 system (San Bruno, CA, USA) with Agela silica gel (Wilmington, DE, USA) (12 g or 20 g, 230–400 μm) cartridges. The μw reactions were performed on a Biotage Initiator 8 system (Charlotte, NC, USA). NMR, LC-MS, and HRMS spectra for the representative final compounds can be found in the supporting information.

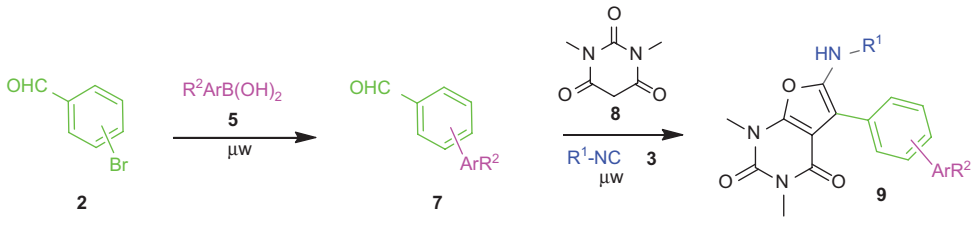
2.2 Synthesis of furocoumarins and furoquinolones 6

2.2.1 Representative procedure for the synthesis of compound 6a

In a 10 ml μw vial equipped with a magnetic stirrer, a mixture of 4-hydroxycoumarin (0.162 g, 1.0 mmol), 4-bromobenzaldehyde (0.185 g, 1.0 mmol) and cyclohexyl isocyanide (0.124 g, 1.15 mmol) was mixed with 0.40 ml of toluene. The mixture was heated under μw at 80°C for 20 min to give **4a**. To the same reaction vial, phenyl boronic acid (0.181 g, 1.5 mmol), Pd(dppf)Cl_2 (0.040 g, 3 mol%), Cs_2CO_3 (0.650 g, 2.0 mmol), and 0.40 ml of 4:4:1 acetone/toluene/water were added. The mixture was heated under μw at 130°C for 20 min. The reaction mixture was filtered and the filtrate was concentrated to give the crude product. Purification of the crude product by flash column chromatography (7:3 hexanes/EtOAc) gave **6a** (0.296 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.14 (m, 2 H), 7.61–7.58 (m, 2 H), 7.50–7.20 (m, 9 H), 3.64–3.42 (m, 1 H), 2.01 (d, *J*=11.7 Hz, 2H), 1.70 (d, *J*=13.4 Hz, 2 H), 1.58 (d, *J*=12.5 Hz, 1 H), 1.21 (ddd, *J*=40.4, 19.9, 7.8 Hz, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.6, 34.3, 53.8, 97.4, 111.0, 112.9, 117.0, 119.6, 124.3, 125.7, 127.4, 127.4, 127.7, 128.5, 128.8, 128.9, 129.2, 131.2, 141.2, 141.6, 150.0, 151.4, 155.1. LC-MS (APCI+): *m/z*=436 $[M+1]^+$. HRMS (ES+): *m/z* [M+H]+ calcd for $C_{29}H_{26}NO_3$: 436.1906; found: 436.1913.

2.2.2 Representative procedure for the synthesis of compound 9a

In a 10 ml μw vial equipped with a magnetic stirrer, 0.40 ml of 4:4:1 acetone/toluene/water was added to a mixture of 4-bromobenzaldehyde (0.185 g, 1.0 mmol), 4-methoxy phenyl boronic acid (0.181 g, 1.5 mmol), Pd(dppf)Cl_2 (0.040 g, 3%), and Cs_2CO_3 (0.650 g 2.0 mmol). The mixture was heated under μw at 130°C for 20 min. The reaction mixture was filtered and the filtrate was concentrated to give the crude product. Purification of the crude product by flash column chromatography (7:3 hexanes/EtOAc) gave **7a** (0.202 g, 95%). A mixture of **7a** (0.106 g, 0.5 mmol), 1,3-dimethylbarbituric acid (0.078 g, 0.5 mmol), and 4-chlorobenzyl isocyanide (0.086 g, 0.57 mmol) in 0.40 ml of toluene was heated under μw at 80°C for 20 min. The crude product was filtered and washed with a minimum amount of toluene to give **9a** as a yellow solid (0.232 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.19 (m, 4 H), 7.50–7.20



Scheme 2 Synthesis of furopyrimidines.

(m, 8 H), 4.21 (d, 2 H), 4.06 (m, 1 H), 3.44 (s, 3H), 3.31 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.2, 28.4, 29.5, 51.1, 96.3, 100.4, 118.1, 126.9, 127.9, 127.9, 128.8, 128.9, 129.6, 129.6, 137.2, 138.1, 138.5, 139.9, 149.0, 150.5, 150.7, 152.8, 158.3. LC-MS (APCI+): m/z=486 $[M+1]^+$.

3 Results and discussion

3.1 Optimization of the MCR for the synthesis of furocoumarin 4a

The MCR of 4-hydroxycoumarin **1a** with 4-bromobenzaldehyde **2a** and cyclohexyl isocyanide **3a** for the synthesis of furocoumarin **4a** was optimized using different solvents and under different reaction temperature and times [14, 15] (Table 1). Toluene was found to be a good solvent for the MCR (Table 1). The next step Suzuki coupling also used toluene as a solvent. It was found that the MCR gave unexpected non-condensed byproducts in polar solvents such as MeOH, EtOH, and DCM-MeOH (Table 1).

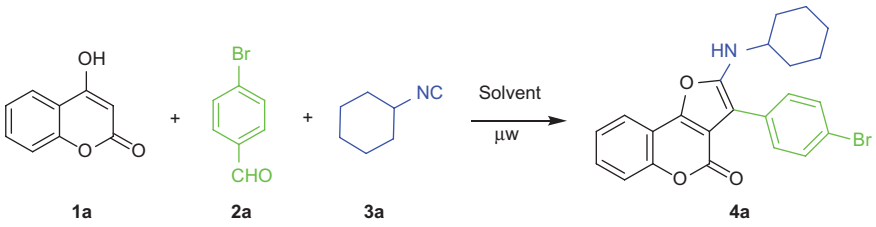
3.2 One-pot MCR and Suzuki coupling for the synthesis of furocoumarins and furoquinolones 6

The one-pot synthesis of compounds **6** were accomplished by the MCR followed by the Suzuki coupling reactions (Table 2). The optimized MCR was carried under μw heating at 80°C for 15 min to obtain furocoumarins **4** with >96% conversion, as detected by LC-MS. It was found that cycloaddition reactions for the furoquinolone intermediate **4f** using *N*-methyl quinolone required more time and a higher temperature for completion. Sequential Suzuki coupling reactions of **4** with phenyl boronic acids [16] to form **6** were conducted in the same vial, without isolation of the intermediate. The Suzuki reactions were carried out using $Pd(dppf)Cl_2$ as a catalyst, 4:4:1 acetone/toluene/water as a co-solvent, and Cs_2CO_3 as a base under μw heating at 130°C for 30 min. Fourteen compounds **6** were prepared in 40–70% yields after flash chromatography purification. The structures of the final products were characterized by LC-MS, ^{1}H and ^{13}C NMR analysis.

3.3 Synthesis of furopyrimidine derivatives 9

We also attempted the synthesis of furopyrimidine derivative **9a** by the one-pot MCR and Suzuki coupling reaction sequence. The MCR of 1,3-dimethylbarbituric acid with 4-bromobenzaldehyde and cyclohexyl isocyanide afforded the desired product **10** in 94% yield. However, the Suzuki reaction of **10** under our conditions was not able to give the product **9a** (Table 3). The furopyrimidine ring was decomposed during the reaction. We developed an alternative pathway for the synthesis of **9** by first performing the Suzuki coupling reaction of 4-bromobenzaldehyde **2a** with the boronic acid. The

Table 1 Optimization of multicomponent reaction (MCR) for the synthesis of furocoumarin **4a.**

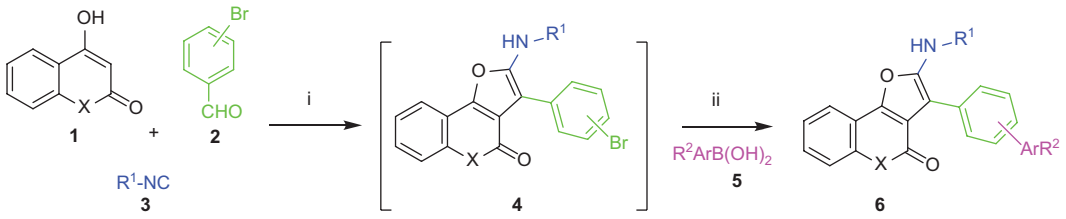


1a **2a** **3a** **4a**

Entry	Solvent	Temp (°C)	Time (min)	Yield (%)[a]
1	DMF	100	10	85
2	DMF	120	10	88
3	Toluene	80	15	97
4	Toluene	120	10	95
5	EtOH	80	15	Uncondensed product[b]
6	MeOH	80	15	Uncondensed product[b]
7	DCM-MeOH	80	15	Uncondensed product[b]

[a]Isolated yield.
[b]Reaction with 1,3-dimethylbarbituric acid.
DMF, N,N-Dimethylformamide; DCM, Dichloromethane.

Table 2 One-pot synthesis of furocoumarin and furoquinolone derivatives **6**.



i) Toluene, μw 80°C, 15 min; ii) $Pd(dppf)Cl_2$, Cs_2CO_3, 4:4:1 acetone/toluene/water, μw 130°C, 20 min

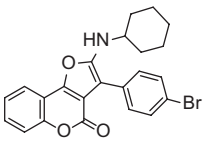
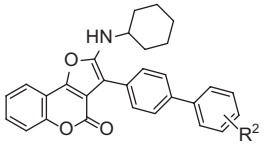
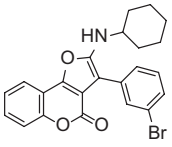
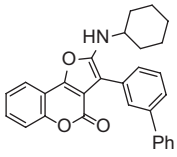
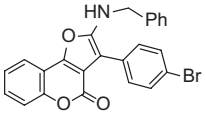
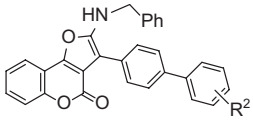
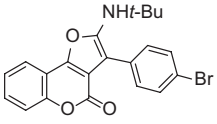
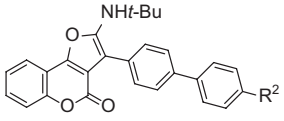
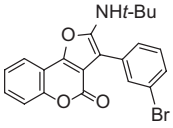
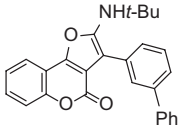
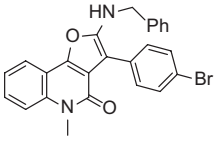
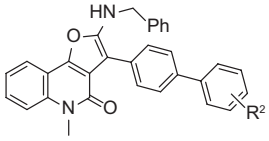
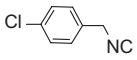
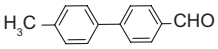
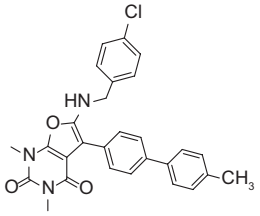
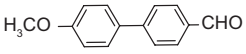
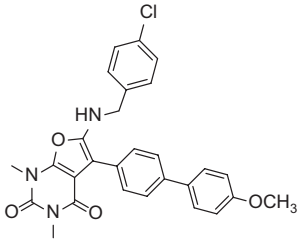
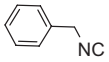
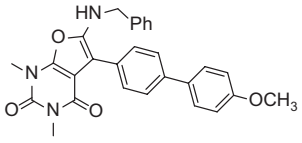
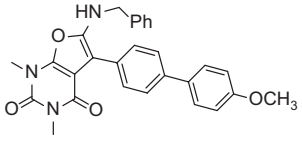
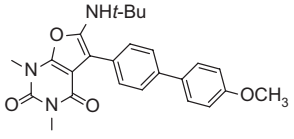
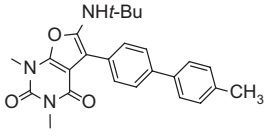
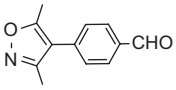
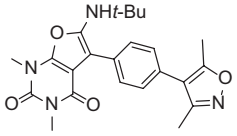
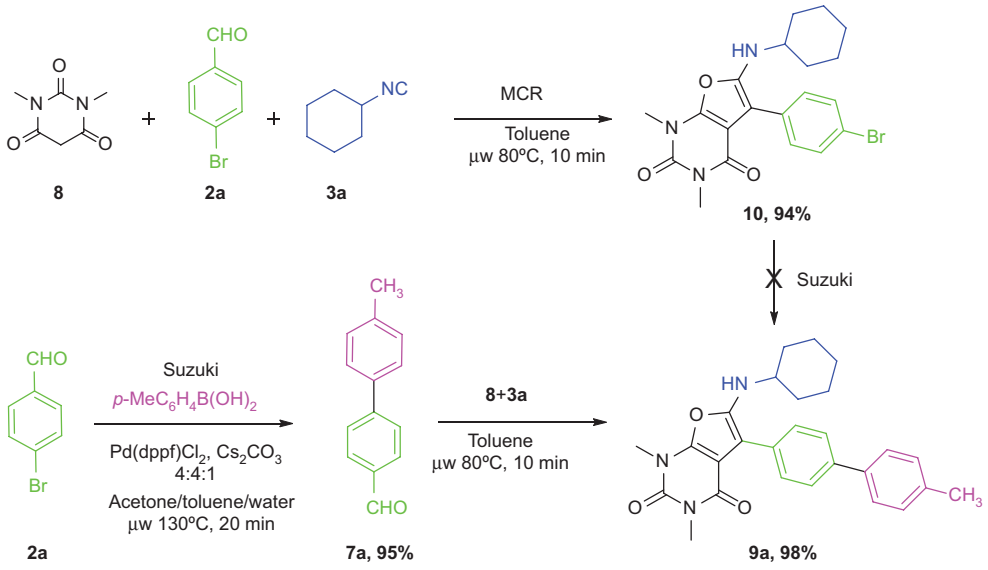
Entry	Intermediate 4	Boronic acid 5	Product 6	Yield (%)
				
1	**4a**	$PhB(OH)_2$	**6a**, R^2=H	68
2	**4a**	*p*-$MeOC_6H_4B(OH)_2$	**6b**, R^2=OCH_3	61
3	**4a**	*p*-$MeC_6H_4B(OH)_2$	**6c**, R^2=CH_3	59
4	**4a**	*m*-$ClC_6H_4B(OH)_2$	**6d**, R^2=Cl	67
				
5	**4b**	$PhB(OH)_2$	**6e**	60
				
6	**4c**	$PhB(OH)_2$	**6f**, R^2=H	60
7	**4c**	*p*-$MeOC_6H_4B(OH)_2$	**6g**, R^2=OCH_3	40
8	**4c**	*p*-$MeC_6H_4B(OH)_2$	**6h**, R^2=CH_3	52
9	**4c**	*m*-$ClC_6H_4B(OH)_2$	**6i**, R^2=Cl	66
				
10	**4d**	$PhB(OH)_2$	**6j**, R^2=H	50
11	**4d**	*p*-$MeOC_6H_4B(OH)_2$	**6k**, R^2=OCH_3	57
				
12	**4e**	$PhB(OH)_2$	**6l**	57
				
13	**4f**	*m*-$ClC_6H_4B(OH)_2$	**6m**, R^2=Cl	62
14	**4f**	*p*-$MeOC_6H_4B(OH)_2$	**6n**, R^2=OCH_3	70

Table 3 Synthesis of furopyrimidine derivatives **9.**

Entry	Isocyanide 3	Bromobenzaldehyde 7	Product 9	Yield (%)
1	 **3b**	 **7a**	 **9a**	98
2	**3b**	 **7b**	 **9b**	97
3	 **3c**	**7b**	 **9c**	99
4	**3c** *t*-BuNC	**7b**	 **9d**	98
5	**3d**	**7b**	 **9e**	96
6	**3d**	**7a**	 **9f**	96
7	**3d**	 **7c**	 **9g**	95



Scheme 3 Synthesis of pyrimidine compound **9a.**

coupling product **7a** was then used for the MCR with 1,3-dimethylbarbituric acid **8** and cyclohexyl isocyanide **3a** under μw heating at at 80°C for 20 min to give **9a** in 98% yield (Scheme 3). Using this approach, we completed the synthesis of seven furopyrimidine derivatives **9a–g** in 95–98% yields.

4 Conclusions

In summary, we have developed an atom- and step-efficient synthesis of biaryl substituted furocoumarin and *N*-methyl quinolone derivatives **6**, by conducting a sequential three-component reaction and the Suzuki coupling reaction in one pot. We also developed an alternative method for the synthesis of furopyrimidine derivatives **9**, by conducting the Suzuki reaction first followed by the three-component reaction. All the reactions were conducted under μw heating to further increase the reaction efficiency.

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