Three-Component One-Pot Approach to Synthesize Benzopyrano[4,3-*d*]pyrimidines

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A novel benzopyrano[4,3-*d*]pyrimidine scaffold was generated via a three-component one-pot reaction from iodochromone, alkyne, and an amidine through a Sonogashira coupling, condensation, and cycloaddition. This combinatorial synthetic approach provides an efficient, easy construction of a diversified heterocyclic compounds library.

Introduction

High-throughput screening (HTS) is employed extensively in drug research and discovery. There is a strong desire to develop efficient methods and strategies for the combinatorial synthesis of a diversified small molecules library to fill the compound demands of HTS.[1] To this end, many efficient synthetic methods have been developed,[2] and one attractive approach is the designation and development of an easily prepared substrate with multireactive sites to promote cascade reactions[3] or multicomponent reactions[4] in one-pot process since such a chemical operation would allow for the generation of a large number of diversified complex molecules with a high efficiency.

Benzopyrano[4,3-*d*]pyrimidine is an important pharmacophore that exhibits anti-inflammatory, antiplatelet, and antithrombotic activities.[5] Relatively few papers have reported on the formation of benzopyrano[4,3-*d*]pyrimidines with a limited substitution from 3-formylchromone or its equivalents by condensation.[6] Herein, we report on an efficient combinatorial synthesis of substituted benzopyrano[4,3-*d*]pyrimidines from a three-component one-pot tandem process in good to excellent yields.

Results and Discussion

Chromone, as a 1,3-diketone equivalent, can be condensed with amidine to form *o*-hydroxyphenyl pyrimidine.[7] We envisioned the hydroxyl group of phenol as being a nucleophile that could take place in a further nucleophilic cyclization with an adjacent triple bond to generate a benzopyrano[4,3-*d*]pyrimidine scaffold from intermediate **A**, which could be generated from iodochromone, alkyne, and amidine through a Sonogashira coupling/condensation/cycloaddition (Path A) or a condensation/Sonogashira coupling/cycloaddition (Path B). In this one-pot process, the palladium species could play a dual role as (i) a Sonogashira coupling catalyst and (ii) as an activating reagent for the triple bond, and a large number of benzopyrano[4,3-*d*]pyrimidines with three diversified positions could be constructed efficiently (Scheme 1).

We evaluated the cascade reaction of iodochromone **1**{*1*} with phenylacetylene **2**{*1*} and methyl carbamimidate sulfate **3**{*1*} under the different conditions (Table 1) to identify the appropriate reaction conditions for this hypothesis. Only intermediate **B** was detected when the reaction, catalyzed by $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %) in the presence of Et_3N or DIPEA (4.0 equiv) as a base, was carried out at room temperature for 2 h. On increasing the reaction temperature to 60 °C and stirring for 6 h, the desired product **4**{*1,1,1*} was not observed, and the reaction was maintained at the stage of intermediate **B** alone (Table 1, entries 1 and 2). We speculated that Et_3N or DIPEA as a weak organic base could not promote the condensation reaction to form intermediate **A** and process the final cyclization. When employed DBU as a strong base, the desired product **4**{*1,1,1*} was obtained in 30% yield, along with the dimeric byproduct of B[8] (Table 1, entry 3). On changing the base to inorganic

Scheme 1. Designed Tandem Process to Form Benzopyrano[4,3-*d*]pyrimidines

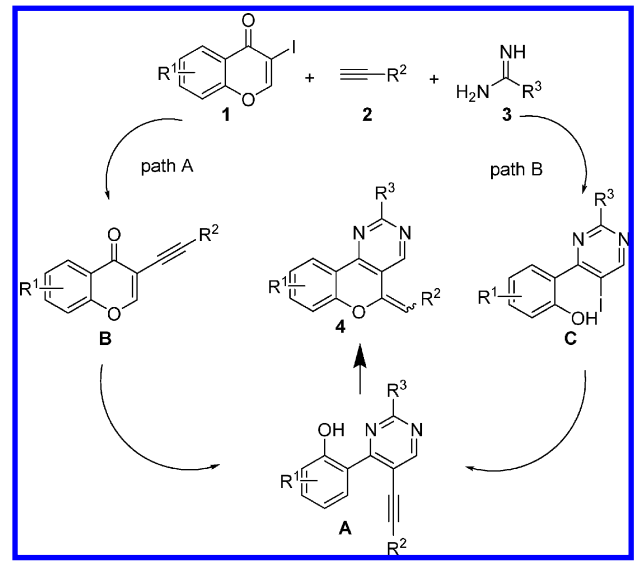

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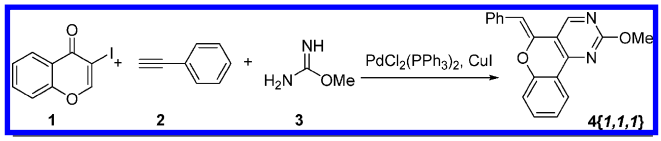
Table 1. Screening Solvent Systems and Bases for the One-Pot Reaction[a]



entry	base	solvent	yield (%)[b]
1	Et_3N (4.0 equiv)	DMF	0
2	DIPEA (4.0 equiv)	DMF	0
3	DBU (4.0 equiv)	DMF	30
4	K_2CO_3 (4.0 equiv)	DMF	63
5	Cs_2CO_3 (4.0 equiv)	DMF	25
6	NaOH (4.0 equiv)	DMF	7
7	DIPEA (2.0 equiv) + K_2CO_3 (4.0 equiv)	DMF	85
8	DIPEA (2.0 equiv) + K_2CO_3 (4.0 equiv)	Toluene	25
9	DIPEA (2.0 equiv) + K_2CO_3 (4.0 equiv)	THF	48
10	DIPEA (2.0 equiv) + K_2CO_3 (4.0 equiv)	CH_3CN	48

[a] Reaction conditions: A mixture of 0.20 mmol 1{1}, 1.5 equiv. of **2**{*1*}, 1.5 equiv. of **3**{*1*}, 5 mol % $PdCl_2(PPh_3)_2$, and 10 mol % CuI in solvent (2.0 mL) was heated at 60 °C for 6 h. [b] Isolated yield based on iodochromone. DIPEA = *N*,*N*-diisopropylethylamine, THF = tetrahydrofuran, and DMF = *N*,*N*-dimethylformamide.

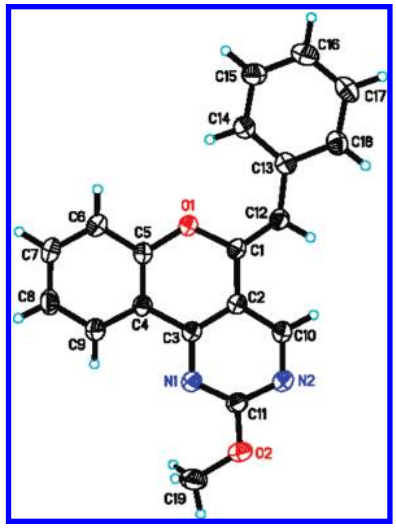


Figure 1. ORTEP plot of **4**{*1*,*1*,*1*} shown with ellipsoids at the 50% level.[9]

K_2CO_3, the yield of **4**{*1*,*1*,*1*} was improved to 63% significantly (Table 1, Entry 4). Other inorganic bases, such as Cs_2CO_3 and NaOH, gave the product in low yield. The combination of DIPEA (2.0 equiv) and K_2CO_3 (4.0 equiv) promoted the reaction smoothly to give the product in 85% yield (Table 1, entry 7). A control experiment was carried out using a mixture of iodochromone **1**{*1*} with methyl carbamimidate sulfate **3**{*1*} (1.5 equiv) with DIPEA (2.0 equiv) and K_2CO_3 (4.0 equiv) in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %) in DMF at room temperature for 2 h, and no intermediate **C** was detected. After the addition of phenylacetylene **2**{*1*}, intermediate **B** was formed the final product was obtained by heating the mixture at 60 °C. This result showed that pathway A is the major pathway for forming the designed product. DMF was found to be the best solvent system on screening other solvents for the reaction. The configuration of the product **4**{*1*,*1*,*1*} was unambiguously established as the Z form from X-ray crystal structure analysis (Figure 1).

To inspect this approach, particularly with regard to library construction, this methodology was evaluated using different

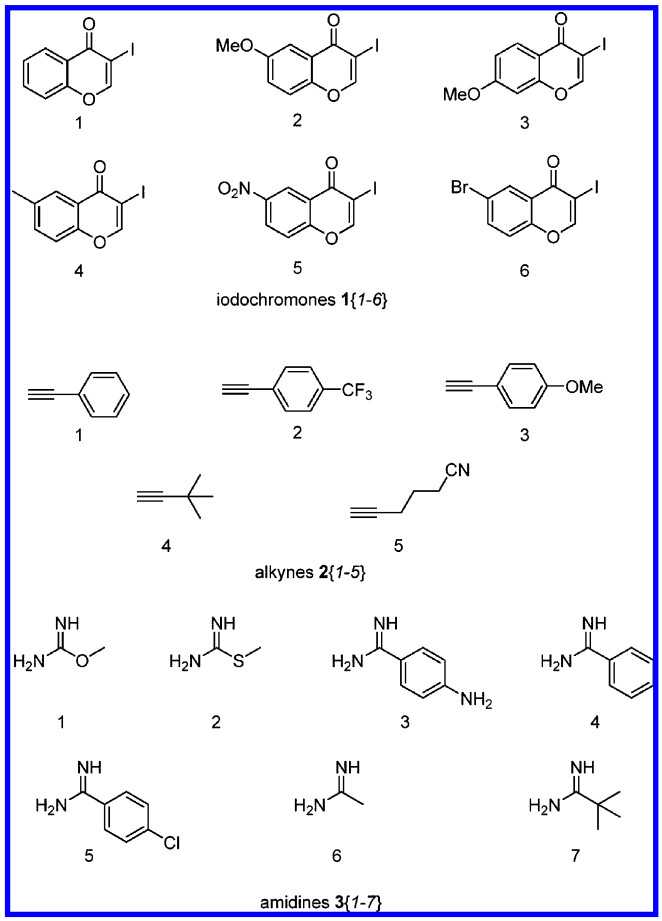
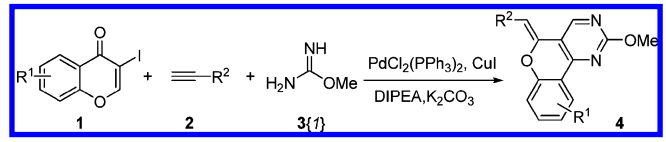


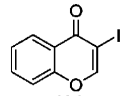
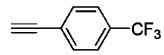
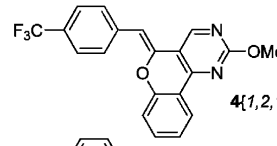
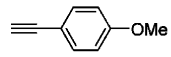
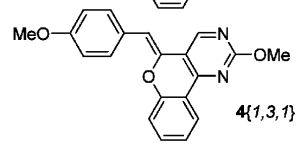
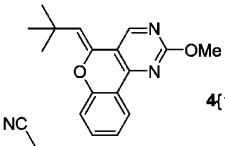
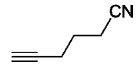
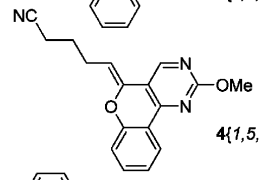
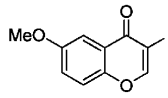
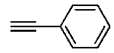
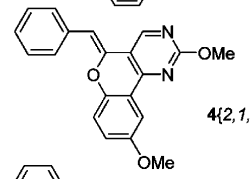
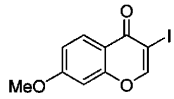
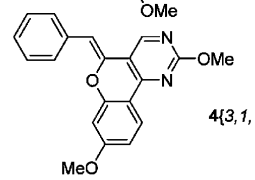
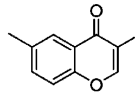
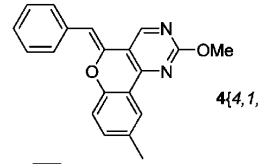
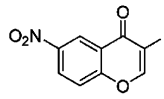
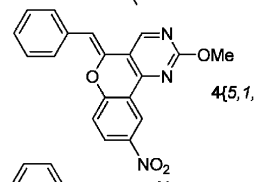
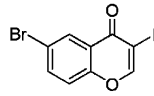
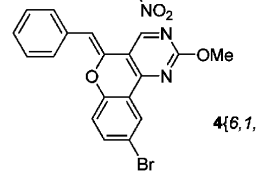
Figure 2. Chemsets employed in the Sonogashira coupling/condensation and cycloaddition protocol.

substituted iodochromones[10] and alkynes (Figure 2) with **3**{*1*} under the optimized reaction conditions. The results are shown in Table 2. On changing the electronic and steric properties (R^2) on the acetylene moiety the corresponding products were afforded in moderate to good yields (Table 2, entries 1−4). An electron-donating group (R^1 = OMe) at the 6-position or 7-position of iodochromone (Table 2, entries 5 and 6) gave the corresponding product in a reasonable yield. Apparently, an electron-withdrawing group ($R^1 = NO_2$ or Br) at the 6-position of iodochromone (Table 2, Entries 8 and 9) afforded complicated products, and isolated **4**{*5*,*1*,*1*} and **4**{*6*,*1*,*1*} in 15% and 18% yields, respectively.

When the reaction was extended to other amidines **3**{*2*−*7*} (Figure 2), only **3**{*2*} and **3**{*3*} was successfully transformed to the corresponding product in 65% and 68% yield, respectively. It is worth noting that amidines **3**{*1*−*3*} with an electron-donating group preceded the formation of the desired product in one-pot tandem process smoothly. Amidines **3**{*4*−*7*} gave only a trace amount of the desired product. On carefully checking the reaction process, we did not find the formation of intermediate **B** at room temperature. On heating the reaction mixture, a small amount of the desired product was generated with a polar major product **5**, which was identified as an imidazole scaffold. A plausible reaction mechanism is shown in Scheme. 2. Under basic conditions, amidines without an electron-donating group can directly undergo a Michael addition with iodochromone and pyrone ring-opening to produce the intermediate **D**. An intramo-

Table 2. Reaction of Various Iodochromones **1** and Alkynes **2** with Methyl Carbamimidate **3**{*1*}[a]



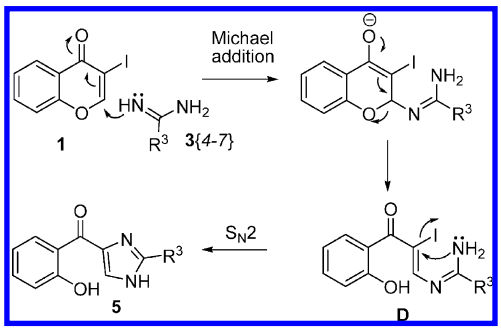
Entry	Substrate 1	Substrate 2	Product 4	Yield(%)[b]
1	 1{1}	 2{2}	 4{1,2,1}	61
2	1{1}	 2{3}	 4{1,3,1}	75
3	1{1}	2{4}	 4{1,4,1}	74
4	1{1}	 2{5}	 4{1,5,1}	48
5	 1{2}	 2{1}	 4{2,1,1}	45
6	 1{3}	2{1}	 4{3,1,1}	43
7	 1{4}	2{1}	 4{4,1,1}	66
8	 1{5}	2{1}	 4{5,1,1}	15
9	 1{6}	2{1}	 4{6,1,1}	18

[a] Unless otherwise stated, the reaction was carried out using Method A. [b] Isolated yield based on iodochromone **1**.

lecular S_N2 reaction with iodide instead of condensation with a carbonyl group would generate imidazole **5** as the major pathway.

A sequential process was applied, where a mixture of iodochromone **1**{*1*} and alkyne **2**{*1*} was stirred under the Sonogashira coupling conditions for 2 h at ambient temperature, followed by addition with different amidines and K_2CO_3. The reaction mixture was heated at 60 °C for 6 h to give the desired product **4**{*1*,*2*−*7*} in good to excellent yields (Table 3). The 1D-NOEDIFF of **4**{*1*,*1*,*7*} was further confirmed the Z configuration (>95%) of the desired product. The condensation and cycloaddition proceeded well without

Scheme 2. Plausible Reaction Mechanism to Generate **5**



the electronic and steric affect of the substituent amidines after the Sonogashira coupling. When applied this sequential one-pot process to the different alkynes and iodochromones, the yields of the reactions in Table 2 were increased to 55%−90%. In particular, substrates **1**{*5*} and **1**{*6*} gave the corresponding product **4**{*5*,*1*,*1*} and **4**{*6*,*1*,*1*} in 55% and 60% yields. From our investigation, this sequential one-pot process should generate a broad substituted benzopyrano[4,3-*d*]pyrimidines library with three diversified points efficiently.

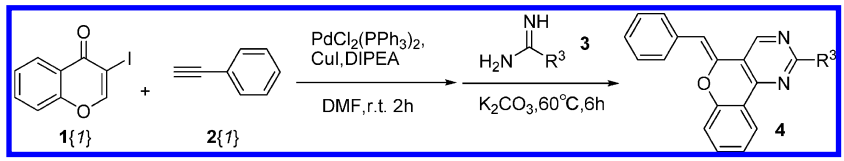
Conclusion

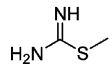
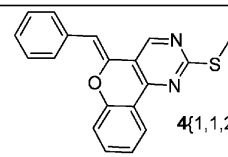
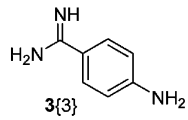
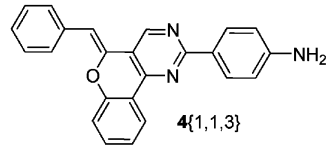
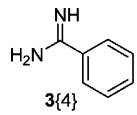
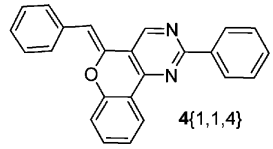
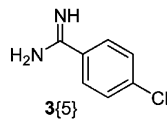
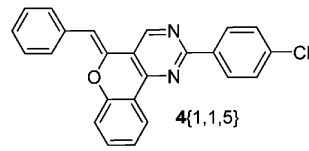
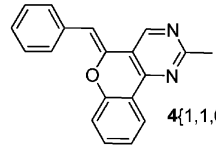
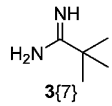
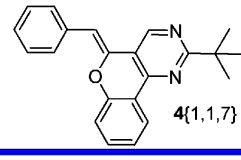
In conclusion, we have developed an efficient approach to generate a diversified benzopyrano[4,3-*d*]pyrimidines library in moderate to good yields via a sequential one-pot reaction of iodochromones, alkynes, and amidines by a Sonogashira coupling, condensation, and cycloaddition. Further library generation and biological evaluation of these compounds is currently under way.

Experimental Section

Method A for the Synthesis of Benzopyrano[4,3-*d*]pyrimidine. Iodochromone (0.2 mmol), alkyne (1.5 equiv), $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.02 mmol), amidine (1.5 equiv), and mixed bases of DIPEA (2.0 equiv) and K_2CO_3 (4.0 equiv) were dissolved in DMF (2.0 mL). The mixture was stirred at room temperature for 2 h and then heated at

Table 3. Reaction of Iodochromone **1**{*1*}and Ethynylbenzene **2**{*1*}with Various Amidines **3**[a]



Entry	Substrate **3**	Product **4**	Yield(%)[b]
1	 **3**{2}	 **4**{1,1,2}	86 (65)[c]
2	 **3**{3}	 **4**{1,1,3}	84 (68)[c]
3	 **3**{4}	 **4**{1,1,4}	92
4	 **3**{5}	 **4**{1,1,5}	74
5	**3**{6}	 **4**{1,1,6}	61
6	 **3**{7}	 **4**{1,1,7}	60

[a] Unless otherwise stated, the reaction was carried out using method B. [b] Isolated yield based on iodochromone **1**{*1*}. [c] The yield in parentheses was obtained according to method A.

60 °C for 6 h. The reaction was monitored by TLC. After the reaction was complete, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (25 mL × 3), and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified by column chromatography.

(*Z*)-5-Benzylidene-2-phenyl-5*H*-benzopyrano[4,3-*d*]pyrimidine 4{*1,1,1*}. With **1**{*1*}, **2**{*1*}, and **3**{*1*} as substrates, method A was followed then the product was purified by column chromatography (silica gel, 15:1 petroleum ether/ethyl acetate) to afford **4**{*1,1,1*} (85%) as a bright yellow solid. Melting point: 128−130 °C. ^{1}H NMR(300 MHz,$CDCl_3$): $\delta = 4.12$ (s, 3H) 6.11 (s, 1H) 7.10−7.18 (m, 2H), 7.21−7.25 (m, 1H), 7.35−7.50 (m, 3H), 7.78 (d, $J = 7.62$ Hz, 2H), 8.27 (dd, $J = 7.92$, 1.76 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.4$, 155.3, 155.2, 154.8, 144.3, 134.7, 133.8, 128.6, 128.4, 126.5, 124.9, 123.1, 118.4, 116.3, 115.4, 102.9, 55.2. MS (ESI): *m/z* 303.1 $(M + H)^+$. HRMS (ESI) calcd for $C_{19}H_{15}N_2O_2$ $(M + H)^+$: 303.1128; found 303.1128.

Method B for the Synthesis of Benzopyrano[4,3-*d*]pyrimidine. Iodochromone (0.2 mmol), alkyne (1.5 equiv), $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.02 mmol), and DIPEA (2.0 equiv) were dissolved in DMF (2.0 mL) and stirred at room temperature for 2 h. Then, amidine (1.5 equiv) and K_2CO_3 (4.0 equiv) were added to the mixture, and this was heated at 60 °C for 6 h. The reaction was monitored by TLC. After the reaction was complete, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (25 mL × 3), and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified by column chromatography.

(*Z*)-5-Benzylidene-2-(methylthio)-5*H*-benzopyrano[4,3-*d*]pyrimidine 4{*1,1,2*}. With **1**{*1*}, **2**{*1*}, and **3**{*2*} as substrates, method B was followed then the product was purified by column chromatography (silica gel, 20:1 petroleum ether/ethyl acetate) to afford **4**{*1,1,2*} (86%) as yellow solid. Melting point: 156−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.66$ (s, 3 H), 6.15 (s, 1H), 7.08−7.19 (m, 2H), 7.22−7.28 (m, 1H), 7.35−7.50 (m, 3H), 7.79 (d, $J = 7.62$ Hz, 2H), 8.27 (dd, $J = 8.05$, 1.61 Hz, 1H), 8.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.5$, 155.2, 152.5, 152.2, 144.2, 134.6, 133.7, 128.7, 128.4, 126.7, 124.8, 123.1, 118.3, 116.4, 103.8, 14.3. MS (EI): *m/z* 318, (M^+, 100). HRMS (EI) calcd for (M^+) $C_{19}H_{14}N_2OS$: 318.0827; found 318.0819.

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Supporting Information Available. Representative experimental procedure and mass, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4** and crystallographic data CCDC 772029. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) CCDC 772029 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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