Article

Efficient Synthesis of Spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-tetraones by a One-Pot and Three-Component Reaction

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An efficient one-pot synthesis of novel 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraone derivatives by a three-component condensation reaction of barbituric acids, isatins and cyclohexane-1,3-diones in refluxing water in the presence of *p*-TSA for 10 h is reported. Two cyclohexane-1,3-diones, three barbituric acids, and eight substituted isatins were chosen for the library validation. Reaction of 5,5-dimethyl-cyclohexane-1,3-dione and acenaphthylene-1,2-dione with barbituric acids resulted in the formation of spiro[acenaphthylene-1,5′-chromeno[2,3-*d*]pyrimidine] derivatives.

1. Introduction

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties.[1] Recently multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economy and convergent character,[2] the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of MCRs. Thus, they are perfectly amenable to automation for combinatorial synthesis.[3]

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[4] Therefore it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received special attention.

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[5] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives (**I**) can highly enhance biological activity.[6] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[7]

Pyrimidine (**II**) and its derivatives have been studied for over a century due to a variety of chemical and biological significance. They have been reported as antibacterial, antiviral and antitumor agents.[8] A number of heterocyclic compounds fused with pyrimidines are known for their varied biological acivities.[9] Similarly, chromene derivatives (**III**) are an important class of compounds, widely present in plants, including edible vegetables and fruits.[10] Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease.[11] Synthetic analogues were developed over the years, some of them displaying remarkable effects as pharmaceuticals,[12] including antifungal[13] and antimicrobial activity.[14]

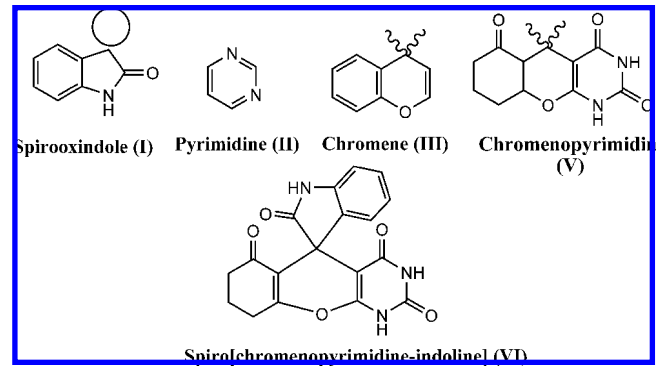

Table 1. Model Reaction, Conditions, and Yield[a]

entry	conditions	catalyst	time (h)	yield (%)
1	CH_3CN (reflux)	*p*-TSA	12	60
2	water (reflux)	*p*-TSA	10	93
3	water/80 °C	*p*-TSA	12	80
4	water (reflux)		24	<40
5	EtOH (reflux)	*p*-TSA	12	83
6	DMF/100 °C	*p*-TSA	12	67
7	MeOH	*p*-TSA	15	58

[a] Barbituric acid (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), isatin (1 mmol), and *p*-TSA (0.1 g).

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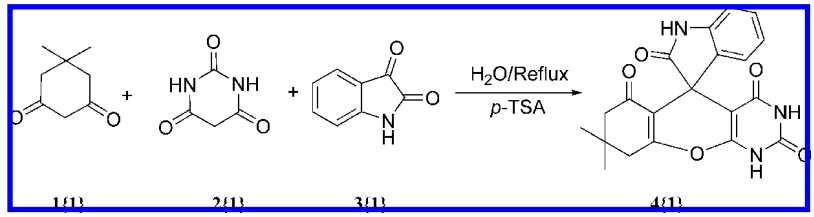
Scheme 1. Model Reaction



Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of spirooxindole heterocycles containing chromenopyrimidine ring fragments (**V**) is therefore an interesting challenge. As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[15] we performed the synthesis of 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraones (**VI**) through a condensation reaction by employing water as the reaction medium. In fact, as clearly stated by R. A. Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water".[16]

2. Results and Discussion

First, to study the reaction in water, we tested the reaction of 5,5-dimethylcyclohexane-1,3-dione **1**{1}, barbituric acid **2**{1}, and isatin **3**{1} as a simple model substrate in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst (Scheme 1). The results are shown in Table 1. It was found that in the presence of *p*-TSA, water is a solvent of choice for the reaction and the desired product obtained in good yield and high purity (entry 2), while without *p*-TSA the yield of product was very low (<40%, entry 4) even after 24 h.

After optimization of the conditions, to delineate this approach, particularly in regard to library construction, this methodology was evaluated by using different barbituric acids, cyclohexane-1,3-diones and isatins. Two cyclohexane-1,3-diones **1**{1,2}, three commercially available barbituric acids **2**{1−3}, and eight substituted isatins **3**{1−8} were chosen for the library validation (Figure 1). Corresponding 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraones **4** were synthesized by the one-

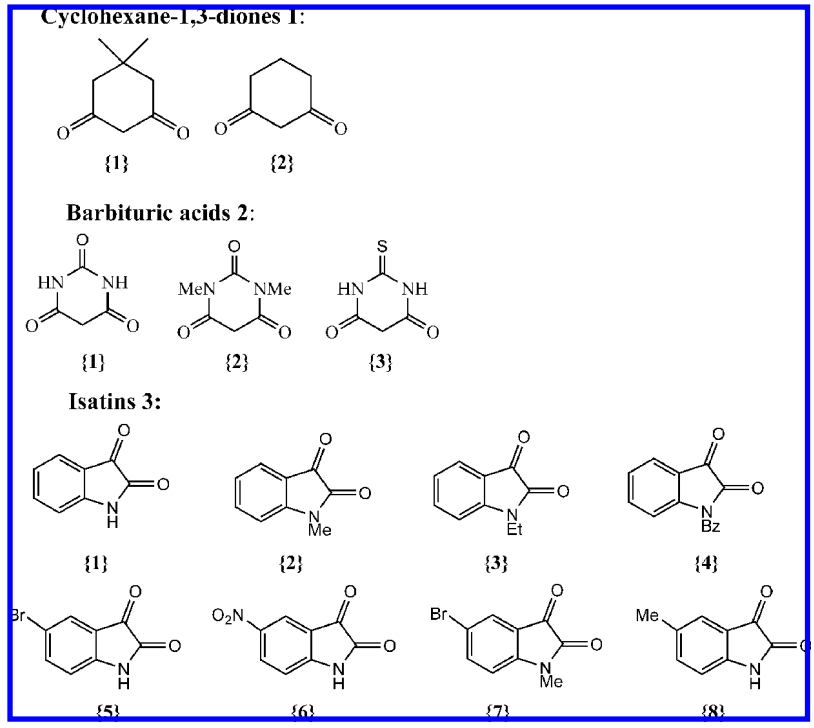


Figure 1. Diversity of reagents.

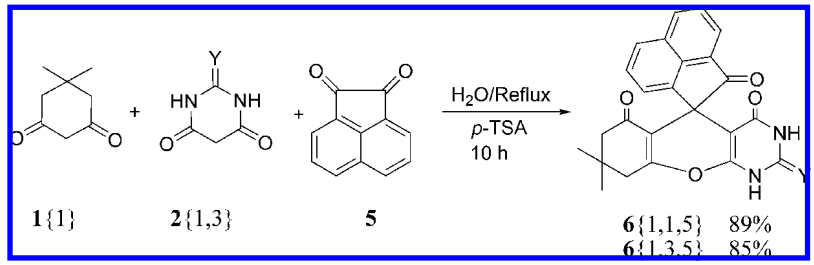
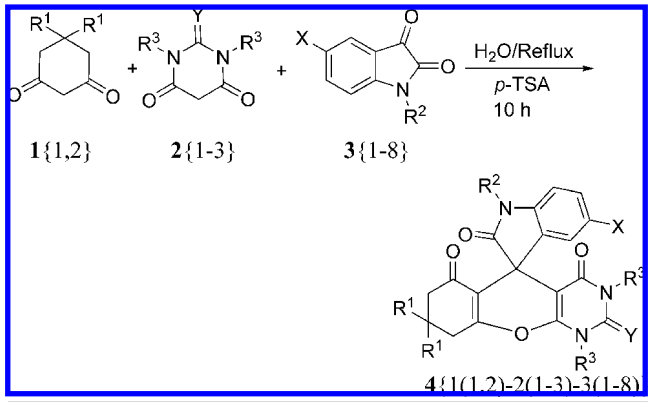


Figure 2. Synthesis of spiro[acenaphthylene-1,5′-chromeno[2,3-*d*]pyrimidine] derivatives **6**.

Table 2. Synthesis of spiro[indoline-pyrazolopyridopyrimidine] derivatives **4**



entry	yield (%)[a]
4{*1,1,1*}	93
4{*1,1,2*}	89
4{*1,1,3*}	88
4{*1,1,4*}	83
4{*1,1,5*}	91
4{*1,1,6*}	95
4{*1,1,7*}	90
4{*1,1,8*}	92
4{*1,2,1*}	80
4{*1,2,2*}	82
4{*1,2,6*}	85
4{*1,3,2*}	85
4{*1,3,5*}	87
4{*1,3,6*}	89
4{*2,1,1*}	87
4{*2,1,2*}	85
4{*2,1,5*}	87
4{*2,1,6*}	89
4{*2,2,2*}	78
4{*2,2,5*}	80
4{*2,2,6*}	82
4{*2,3,1*}	83
4{*2,3,5*}	85
4{*2,3,6*}	85

[a] Isolated yields.

pot, three-component condensation of cyclohexane-1,3-diones **1**, barbituric acids **2** and isatin **3** in good yields at refluxing water in the presence of *p*-TSA for 10 h. The reaction can be represented as in Table 2. To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-tetraone derivatives.

Given the large number of commercially available isatins and the easy access to barbituric acids and cyclic-1,3-diones, the present method should be applicable to synthesis of libraries with high diversity. We expect this method to find extensive application in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Finally, to further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated reaction involving acenaphthylene-1,2-dione **5** and obtained spiro-[acenaphthylene-1,5′-chromeno[2,3-*d*]pyrimidine] derivatives **6** in good yields (Figure 2).

Compounds **4** and **6** are stable solids whose structures were established by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis.

In conclusion, an efficient, clean and simple method for the preparation of 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraones using readily available starting materials is reported. Prominent among the advantages of this new method are novelty, operational simplicity, good yields and easy workup procedures employed.

Experimental Section

Typical Procedure for Preparation of 8,8-Dimethyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraone (4{*1,1,1*}). A mixture of 5,5-dimethyl-cyclohexane-dione (0.14 g, 1 mmol), barbituric acid (0.13 g, 1 mmol), isatine (0.15 g, 1 mmol), and *p*-TSA (0.1 g) in refluxing water (5 mL) was stirred for 10 h. After completion of the reaction confirmed by TLC (eluent EtOAc/*n*-hexane, 1:3), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water (10 mL) and ethanol (5 mL) to afford the pure **4**{*1,1,1*} as a white powder (0.35 g, yield 93%). MP >300 °C. IR (KBr) (ν_{max} /cm^{-1}): 3337, 3265, 1746, 1664, 1620. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.97 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.07, 2.10 (2H, AB_q, $^3J_{AB}$ = 15.9 Hz, CH_2), 2.55, 2.66 (2H, AB_q, $^3J_{AB}$ = 17.6 Hz, CH_2), 6.71 (1H, d,$^3J_{HH}$ = 7.8 Hz H−Ar), 6.78 (1H, t, $^3J_{HH}$ = 7.5 Hz H−Ar), 6.97 (1H, d, $^3J_{HH}$ = 7.5 Hz, H−Ar), 6.08 (1H, t, $^3J_{HH}$ = 7.5 Hz, H−Ar), 10.36(1H, s, NH), 11.01(1H, s, NH), 12.19(1H, brs, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.1, 28.2, 32.2, 45.5, 50.8, 89.6, 109.0, 113.6, 121.3, 123.3, 128.3, 134.0, 144.3, 149.4, 153.5, 161.9, 163.6, 178.2, 195.3. Anal. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.37; H, 4.56; N, 11.00.

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Supporting Information Available. Experimental procedures and IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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