Novel One-Pot, Three-Component Synthesis of Spiro[Indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]trione Library

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A one-pot method for the efficient and simple synthesis of the novel spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]trione derivatives by a three-component condensation reaction of barbituric acids, 1*H*-pyrazol-5-amines and isatins in aqueous media is reported.

1. Introduction

Multicomponent reactions (MCRs) have been designed to produce elaborate biologically active compounds and have become an important area of research in organic, combinatorial, and medicinal chemistry.[1] The MCR strategy offers significant advantages over conventional linear-type synthesis because of its flexible, convergent, and atom efficient nature.[2] In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[3] Thus, the success of combinatorial chemistry in the drug discovery process considerably depends on further advances in the heterocyclic MCR methodology and also the environmentally benign multicomponent procedures.

Pyrimidopyrimidine is a heterocycle that has attracted considerable interest in recent years. Its derivatives, such as pyrimido[4,5-*d*]pyrimidine and pyrimido[2,3-*d*]pyrimidine, have been known to display a wide range of pharmacological activities.[4,5] Pyrimidopyrimidine are also known to be inhibitors of tyrosine kinase of the epidermal growth factor receptor family.[6] Numerous reports delineate the antitumor,[7] antiviral,[8] and antioxidant[9] activity of these compounds. Recently, considerable attention has been focused on the development of new methodologies to synthesize many kinds of pyrazolopyrimidine ring systems.[10] Indeed, these compounds are widely recognized as important organic materials with interesting biological activities.[11] The most important biologically active compounds of this class are the formycin, allopuriol, and their corresponding nucleosides. In addition, fused heterocyclic systems like pyrazolopyridopyrimidines, pyrazoloquinolines, and pyrazolopyridines present interesting biological properties such as virucidal, anticancer, fungicidal, bactericidal. and vasodilatory activities.[12]

The indole moiety is probably the most well-known heterocycle and is a common and important feature of a variety of natural products and medicinal agents.[13] Furthermore, it has been reported that the sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances the biological activity.[14] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[15]

Some indoles or oxindoles that were fused with different heterocyles have recently received attention due to their useful biological properties.[16] These fused-heterocycle systems seem to be promising candidates for biological responses since they incorporate both indole and other heterocycles moieties simultaneously.

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of the spirooxindole heterocycles containing pyrazolopyridopyrimidines ring fragments will be a beneficial and interesting challenge. As a part of our research program, which aims to develop new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[17] herein, we report the synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]triones through a condensation reaction 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".[18] The use of water as a reaction medium represent a remarkable benefit because it is a green solvent and with high polarity is immiscible with the most of organic compounds. Moreover, the water-soluble catalyst resides and operates in the aqueous phase and as a result separation of organic materials is quite easy.

2. Results and Discussion

First, to achieve suitable conditions for the synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]triones **4**, we tested the reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine **1**{*1*}, barbituric acid **2**{*1*}, and isatin **3**{*1*} as a simple model substrate in various solvents and under solvent-free classical heating conditions in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and readily available catalyst (Scheme 1). As is evident from Table 1, in refluxing organic solvents or under solvent-free conditions,

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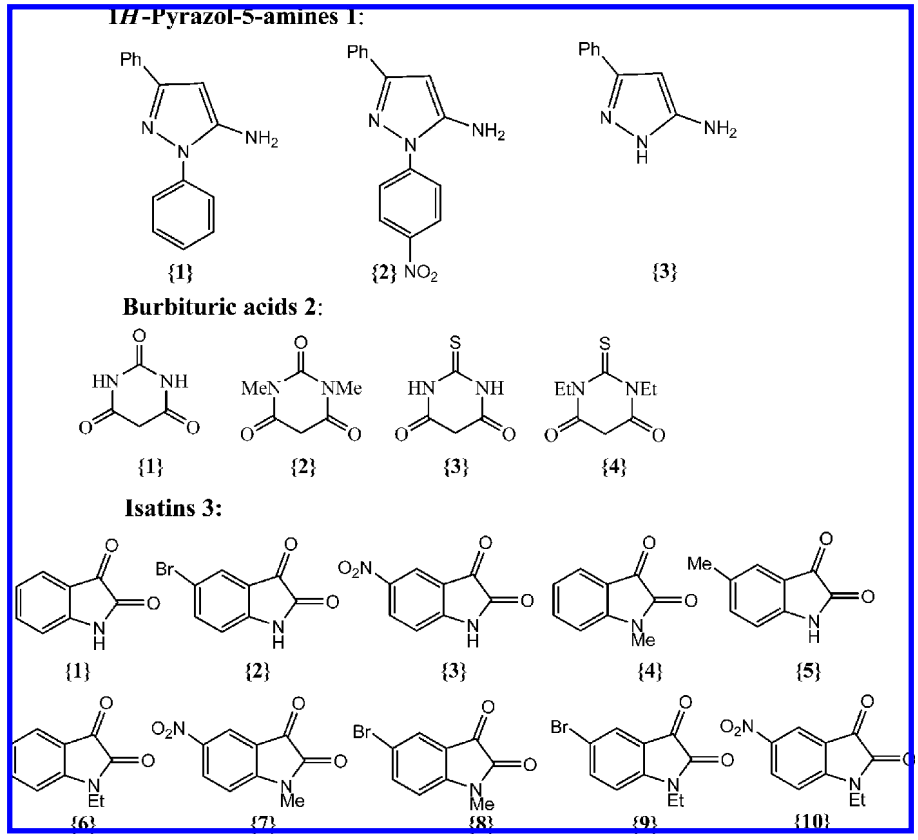


Figure 1. Diversity of reagents.

Scheme 1. Model Reaction

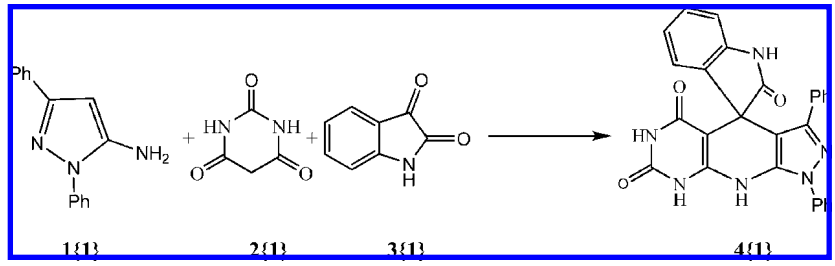


Table 1. Model Reaction, Conditions, and Yield[a]

entry	conditions	catalyst	time (h)	yield (%)
1	solvent-free (100 °C)	*p*-TSA	12	45
2	CH_3CN (reflux)	*p*-TSA	24	40
3	water (reflux)	*p*-TSA	24	90
4	water (reflux)		60	<30
5	EtOH (reflux)	*p*-TSA	24	64
6	DMF (reflux)	*p*-TSA	24	61

[a] Barbituric acid (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), and isatin (1 mmol) and *p*-TSA (0.1 g).

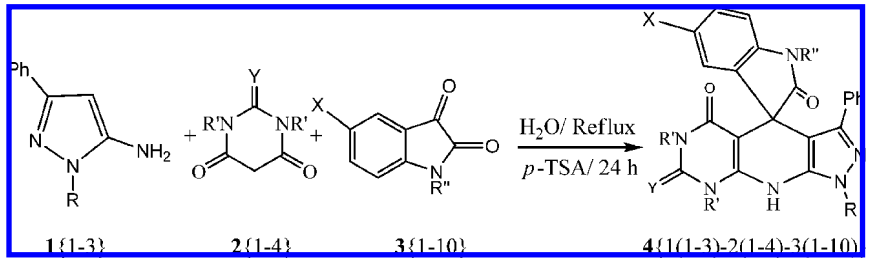
the yield of product was low. It was found that in the presence of *p*-TSA, water is the solvent of choice for the reaction and the desired product was obtained in good yield and high purity (entry 3), while without *p*-TSA and over long period of time (60 h) the yield of product was very low (<30%, entry 4).

Then, to delineate this approach, particularly in regard to library construction, this methodology was evaluated by using different barbituric acids, 1*H*-pyrazol-5-amines and isatins. Three 1*H*-pyrazol-5-amines **1**{*1*−*3*}, four commercially available barbituric acids **2**{*1*−*4*}, and ten substituted isatins **3**{*1*−*10*} were chosen for the library validation (Figure 1). Corresponding spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine] derivatives **4** were selectively synthesized by the one-pot, three-component condensation of 1*H*-pyrazol-5-amines **1**, barbituric acids **2**, and isatin **3** in good yields at refluxing water in the presence of *p*-TSA for 24 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 method for the synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine] derivatives.

Given the large number of commercially available isatins and the easy access to barbituric acids and 1*H*-pyrazol-5-amines, this 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.

We have not established an exact mechanism for the formation of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine] derivatives **4**, however, a reasonable possibility is shown in Supporting Information.

Table 2. Synthesis of Spiro[Indoline-pyrazolopyridopyrimidine] Derivatives **4**



entry	yield (%)[a]
4{*1,1,1*}	90
4{*1,1,2*}	88
4{*1,1,3*}	94
4{*1,1,4*}	96
4{*1,1,5*}	83
4{*1,1,6*}	82
4{*1,1,7*}	87
4{*1,1,8*}	82
4{*1,1,9*}	87
4{*1,1,10*}	84
4{*1,2,2*}	78
4{*1,2,3*}	80
4{*1,2,4*}	85
4{*1,2,8*}	95
4{*1,3,1*}	91
4{*1,3,2*}	92
4{*1,3,3*}	97
4{*1,3,4*}	95
4{*1,3,6*}	98
4{*1,3,8*}	97
4{*2,1,1*}	83
4{*2,1,2*}	87
4{*2,1,3*}	82
4{*2,1,4*}	84
4{*2,1,6*}	87
4{*2,3,2*}	78
4{*3,1,1*}	80
4{*3,1,2*}	87
4{*3,1,3*}	83
4{*3,2,1*}	86
4{*3,2,3*}	81
4{*3,3,1*}	81
4{*3,3,3*}	85
4{*3,4,1*}	80
4{*3,4,2*}	79
4{*3,4,3*}	82

[a] Isolated yields.

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

In conclusion, we have demonstrated an efficient and simple method for the preparation of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine] derivatives using readily available starting materials. Prominent among the advantages of this new method are novelty, operational simplicity, good yields and easy workup procedures employed. Further reactivity studies and synthetic applications of this methodology are in progress in our laboratory.

3. Experimental Section

Typical Procedure for Preparation of 1′,3′-Diphenylspiro[indoline-3,4′-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]-2,5′,7′(6′*H*,8′*H*,9′*H*)-trione (4{*1,1,1*}). A mixture of 1,3-diphenyl-1*H*-pyrazol-5-amine (0.24 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 24 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and ethanol (5 mL) to afford the pure **4**{*1,1,1*} as a white powder (0.43 g, yield 90%). MP >300 °C. IR (KBr) (ν_{max} /cm^{-1}): 3215 (NH), 1737, 1717, 1623. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.50−7.69 (14H, m, H−Ar), 9.36 (1H, s, NH), 9.93 (1H, s, NH), 10.18 (1H, s, NH), 10.67 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 48.3, 88.1, 100.7, 109.4, 121.7, 123.4, 124.1, 127.8, 128.2, 128.3, 128.9, 130.3, 132.9, 136.7, 137.4, 137.9, 142.9, 146.5, 149.8, 149.9, 162.2, 179.1. Anal. Calcd for $C_{27}H_{18}N_6O_3$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.30; H, 3.86; N, 17.65.

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

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