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Synthesis of novel spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3′-indoline]-1,2′,13(2*H*)-triones *via* three component reaction

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ABSTRACT

A new and efficient method for the synthesis of hitherto unreported spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3′-indoline]-1,2′,13(2H)-triones was developed *via* the Domino Knoevenagel condensation–Michael addition–intermolecular cyclization sequences of isatin derivatives, cyclohexane-1,3-diones, and 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones, employing 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) as an effective and inexpensive catalyst.

1. Introduction

Multicomponent reactions (MCRs) have been applied for the synthesis of highly functional complex organic molecules and biologically active heterocyclic compounds from simple and readily available starting materials.[1] These reactions have attracted special attention owing to their simplicity, efficiency, selectivity, convergence, shorter reaction times, atom-economic characteristics, and environmental friendliness.[2] As a powerful and widely employed synthetic protocol, MCRs provide a highly efficient platform for the rapid synthesis of various fused-ring products, in which the formation of two or more new rings is allowed.[3,4] Fused heterocyclic architectures are widespread in natural products and pharmaceutical molecules, revealing their great capacity as a source of novel functional compounds.[5] Spiro compounds as a major class of heterocyclic materials exhibit crucial biological activities.[6,7] Spirocyclic systems have remarkable structures because of their two fused rings through one spiro carbon atom.[8] Spirooxindole is a particularly rare heterocyclic moiety in various natural alkaloids and synthetic molecules and has demonstrated multiple pharmaceutical activities.[9,10] Moreover, spirooxindole moieties appear in natural products, such as spirotryprostatins A and B, which are regularly detected in *Aspergillus fumigatus* for modulating the utility of muscarinic serotonin receptors (Fig. 1 (1, 2)).[11,12]

Thiazolopyrimidine derivatives are crucial scaffolds since they are prominent structural elements of purine bases. These heterocyclic ring systems show several biological activities,[13–18] including anti-cancer,[19] antidiabetic,[20] *anti*-HSV-1,[21] antibacterial, antimicrobial,[22] antioxidant,[23] anti-inflammatory,[24] anti-malarial,[25] *anti*-HIV,[26] herbicidal,[27] antitumor, and anti-human cytomegalovirus (HCMV) activities (Fig. 1 (3–5)).[28,29]

In recent years, heterogeneous catalytic systems have attracted considerable attention because of their easy separation, recyclability of catalysts, and environment friendly reaction conditions. Recently, Keggin-type heteropolyacids (HPAs) as strong Brønsted acids have been extensively studied for organic synthetic processes in homogeneous and heterogeneous media. HPAs are economically and environmentally attractive because of some of their advantages, such as flexible acidic strength, reusability, non-corrosiveness, and environmental compatibility. They are highly soluble in water and polar solvents but insoluble in non-polar solvents.

Furthermore, HPAs, particularly tungstophosphoric acid ($H_3PW_{12}O_{40}$), are stronger acid catalysts than conventional acid catalysts, such as zeolites and ion-exchange resins.[30–32] The assimilation of other heterocyclic platforms into

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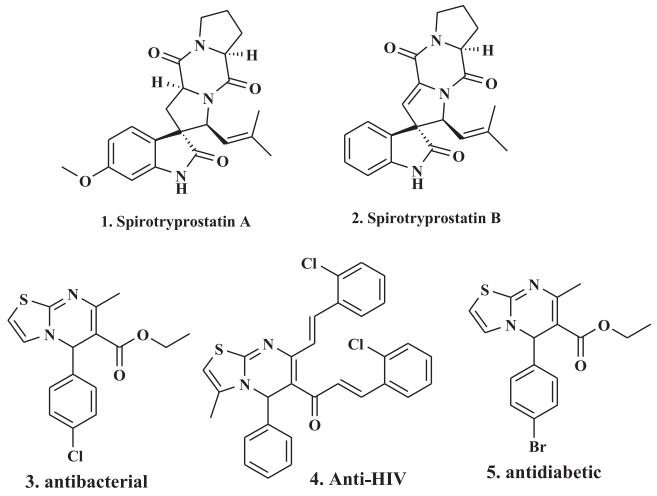


Fig. 1. Some biologically active compounds containing spirooxindole (1, 2) and thiazolopyrimidine (3–5) moiety.

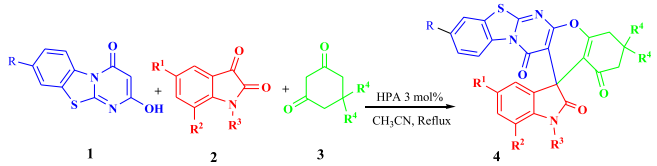
spirooxindoles,[33–37] either in the form of an extra cyclic substituent or as a fused structure, often leads to enhanced biological effects. Taking these into account, as a part of our ongoing program on novel spiro-heterocyclic synthesis,[38–42] we designed a novel hybrid molecule by combining both spirooxindole derivatives and thiazolopyrimidine moiety, which serve as a bridge between chemistry and biology.

Herein, we introduce the synthesis of novel spirooxindole-pyranobenzothiazolopyrimidine derivatives *via* a three-component condensation reaction of isatin derivatives, 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones, and cyclohexane-1,3-diones using tungstophosphoric acid as an efficient promoting catalyst. To the best of our knowledge, this is the first report on the synthesis of spirooxindole pyrimidines using 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones as a heterocyclic-1,3-dion (Scheme 1).

2. Results and discussion

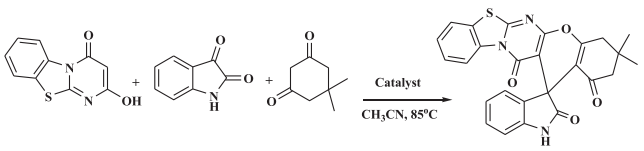
To examine the feasibility of our protocol, we initially explored the reaction of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (**1**), isatin (**2**), and dimedone (**3**) in acetonitrile at reflux in the absence of a catalyst for 24 h, which provided the desired product **4a** in trace amount (Table 1, entry 1). Encouraged by the preliminary result, we investigated various reaction conditions, results of which are summarized in Table 1. The employment of various acids, including acetic acid, *p*-toluenesulfonic acid, and L-Proline, was less effective (Table 1, entries 2–4).

The results revealed that the nature of the acid significantly affected the outcome of the reaction. Among various acids, tungstophosphoric acid ($H_3PW_{12}O_{40}$) provided the best result, with 73% product yield (Table 1, entry 5). Although ionic liquids and sulphuric acid are well-known to be good catalysts for certain organic



Scheme 1. Three component synthesis of spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3′-indoline]-1,2′,13(2*H*)-trione derivatives.

Table 1
Influence of Different Catalysts on the Reaction of 2-Hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one, Isatin and 5,5-Dimethylcyclohexane-1,3-dione[a].



Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	No	24	trace
2	CH_3COOH (10)	24	10
3	PTSA[b] (10)	24	10
4	L-Proline (10)	24	trace
5	$H_3PW_{12}O_{40}$ (3)	10	73
6	[bmim]Br[c]	24	30
7	[bmim][HSO_4][d]	24	60
8	MS 4A°[e]	24	trace
9	H_2SO_4 (3)	24	50

[a] Reaction condition: 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (1 mmol), isatin (1 mmol), 5,5-dimethylcyclohexanedione (1 mmol) in CH_3CN (5 ml) at reflux.
[b] *P*-toluenesulphonic acid.
[c] 1-butyl-3-methylimidazolium bromide (0.2 mmol).
[d] 1-(4-sulfonicacid)butyl-3-methylimidazolium hydrogen sulfate (0.2 mmol).
[e] Molecular sieve 4°A°(0.1 gr).

reactions, their catalytic activities for this reaction were lower than that of $H_3PW_{12}O_{40}$ (Table 1, entries 6, 7, 9). Notably, a trace amount of product **4a** was detected when the reaction was performed in the presence of molecular sieve (MS 4A°) as an additive (Table 1, entry 8).

Then, we assessed different solvents including, ethanol, H_2O, EtOH/H_2O (1:1), DMF, and neat conditions (Table 2, entries 1–5). The results demonstrated acetonitrile to be the best solvent, with 73% yield for the target compound **3a**. The reaction was also monitored under different catalyst loading, and the results revealed that 3 mol% of the catalyst was the optimum loading for completing the reaction. At a lower catalyst loading, the reaction was not completed (Table 2, entry 7). According to results, the efficiency of $H_3PW_{12}O_{40}$ for this reaction was not improved by the increased catalyst loading (Table 2, entries 8, 9). Finally, the optimal conditions were determined as **1** (1 equiv.), **2** (1 equiv.), **3** (1 equiv.), and tungstophosphoric acid ($H_3PW_{12}O_{40}$) (3 mol %) in CH_3CN at reflux for 10 h (Table 2, entries 6).

The optimized reaction conditions were then tested for library construction with two heterocyclic dions 1, seven isatin derivatives 2, and two 1,3-dicarbonyl compounds 3.The results are summarized in Table 3. As shown in Table 3, isatin and its 5-substituted derivatives reacted with 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones and 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione to provide the desired product **4** in good yields (Table 3,compounds **4a**–**f**, **4i**, and**4j**).

Although 5-substituted, *N*-Me isatin derivatives were successfully employed in the reaction (Table 3, compounds **4g**, **4h**), other nitrogen-protected isatin substrates, such as *N*-Et and *N*-benzyl analogs, did not produce satisfactory yields (10% and trace). To our disappointment, no product was detected when 7-bromoistain and 7-chloroisatin were used in the reaction, whereas the respective product was produced with good efficiency using 7-methylisatin (Table 3, compound **4e**). When other cyclic 1,3-dicarbobonyl compounds, such as barbituric acid and 2*H*-indene-1,3-dione, were used, the reaction proceeded, but their complex mixture products could not be purified. Although 5-substituted, *N*-Me isatin derivatives were employed in the reaction successfully (Table 3,