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RESEARCH ARTICLE

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Simple Three-Component Method for the Synthesis of Spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines

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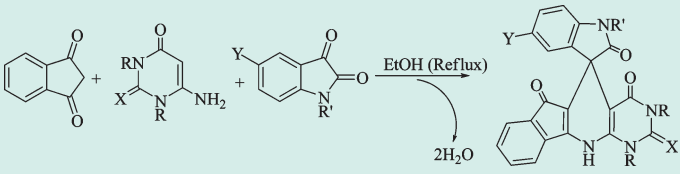
Supporting Information

ABSTRACT: An efficient, simple, and catalyst-free synthesis of spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines and spiroacenaphthylene-1,4′-indeno-1,5′-pyrido[2,3-*d*]pyrimidines by the three-component reaction of 1,3-indandione, amino uracils and isatins or acenaphthylene-1,2-dione in refluxing ethanol is reported.



KEYWORDS: catalyst-free, spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3'-indolines, spiroacenaphthylene-1,4'-indeno-1,5'-pyrido[2,3-*d*]-pyrimidines, amino uracils, isatins, acenaphthylene-1,2-dione

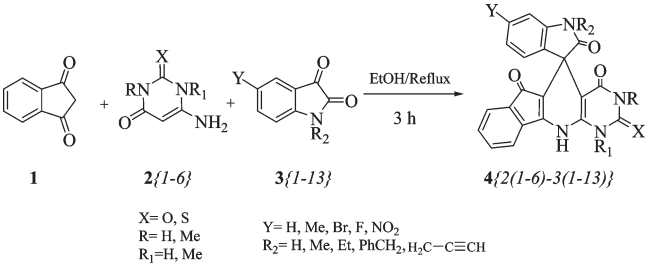
INTRODUCTION

Pyrimidopyrimidines are annulated uracils that have attracted considerable attention in recent years. Their derivatives are known to display a wide range of pharmacological activities,[1] and their potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor,[2] 5-phosphoribosyl-1-pyrophosphate synthetase,[3] and dihydrofolate reductase[4] have been fully demonstrated. Therefore, for the preparation of these complex molecules, significant efforts were directed toward the synthetic manipulation of uracils.[5] Similarly, heterocycles containing indenone moiety are an important class of heterocyclic compounds, since many of these heterocyclic systems exhibit biological and pharmaceutical activity. The indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member onychine.[6] Indenopyrazoles and indenopyridazines have been identified as cyclin-dependent kinase[7] and selective monoamine oxidase B (MAO-B)[8] inhibitors, respectively. Indenoquinoline derivatives have shown a diverse range of biological properties, such as 5-HT-receptor binding and anti-inflammatory activities.[9]

The heterocyclic indole and indoline ring systems are widely distributed structural frameworks that are observed in a number of pharmaceuticals and natural products,[10] and some of indolines, spiro-annulated with heterocycles in the 3-position, are biologically activity.[11] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[12]

Although several isatin-based multicomponent reactions have been reported by our[13] or other research groups[14] for the synthesis of spirooxindoles containing heterocycles, the reaction of amino uracil, isatin and 1,3-diketones has not been reported yet. In this paper, we report an efficient synthesis of spirooxindoles anulated indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine **4** based on a one-pot three-component reaction of 1,3-indandione **1**, amino uracils **2** and isatins **3** (Scheme 1).

Scheme 1. Synthesis of Spiroindeno[1,2-*b*]pyrido[2,3-*d*]-pyrimidine-5,3′-indolines 4



2: Amino uracil derivatives (Fig. 1)
3: Substituted isatins (Fig 2)

RESULTS AND DISCUSSION

A mixture of 1,3-indandione **1**, amino uracils **2**, and isatins **3** in the absence of any catalyst in refluxing ethanol for 3 h, afforded spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines **4** in good yields (Scheme 1).

To obtain spirooxindoles annulated indeno[1,2-*b*]pyrido[2,3-*d*]-pyrimidine, we used six amino uracils **2**{*1*−*6*} and a wide diversity of isatins **3**{*1*−*13*} that the latter contains substitutions in both aromatic nucleus and at N-1 (Figures 1 and 2). In this method, thirty seven new compounds **4** were selectively synthesized by the one-pot, three-component condensation of 1,3-indandione **1**, amino uracils **2**, and isatins **3** in good yields. The results are summarized in Table 1.

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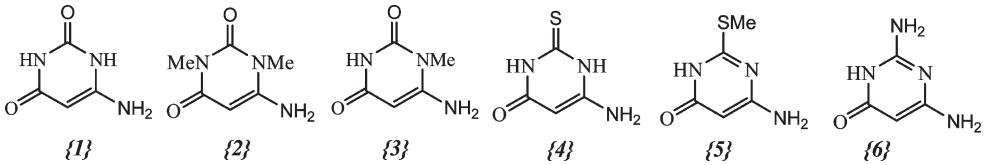


Figure 1. Amino uracils **2**{*1*−*6*}.

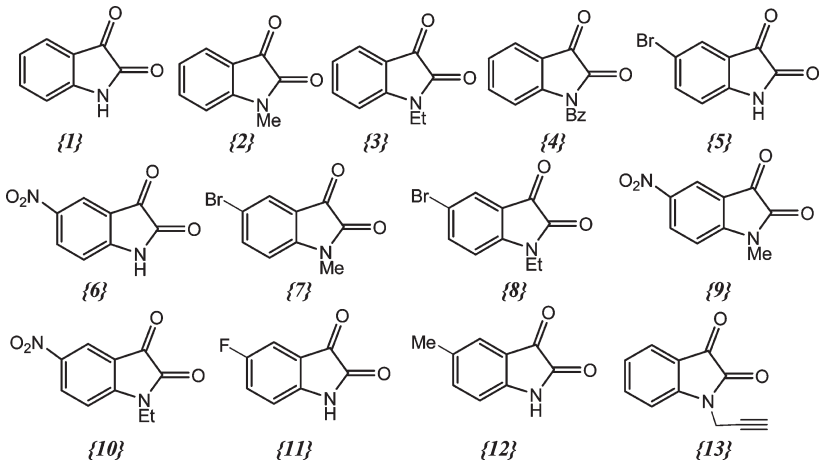


Figure 2. Isatins **3**{*1*−*13*}.

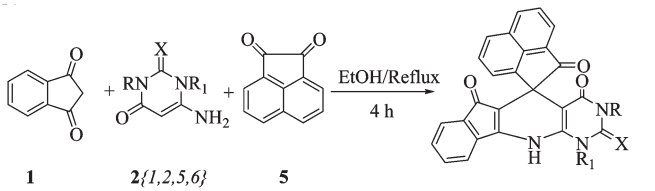
Table 1. Synthesis of Spiroindeno[1,2-*b*]pyrido[2,3-*d*]-pyrimidine-5,3′-indolines 4

entry	yield (%)[a]	purity (%)[b]	entry	yield (%)[a]	purity (%)[b]
4{*1,1*}	93	>95	4{*4,13*}	85	88
4{*1,2*}	80	94	4{*5,1*}	91	91
4{*1,5*}	78	92	4{*5,2*}	87	92
4{*1,6*}	93	93	4{*5,3*}	87	95
4{*2,1*}	89	89	4{*5,5*}	85	92
4{*2,2*}	82	>95	4{*5,6*}	90	89
4{*2,5*}	80	94	4{*6,1*}	95	94
4{*2,6*}	89	90	4{*6,2*}	89	>95
4{*2,13*}	87	88	4{*6,3*}	85	>95
4{*3,1*}	88	88	4{*6,4*}	89	93
4{*3,2*}	85	92	4{*6,5*}	85	94
4{*3,5*}	82	90	4{*6,6*}	95	90
4{*3,6*}	87	94	4{*6,7*}	82	92
4{*3,13*}	89	87	4{*6,8*}	80	94
4{*4,1*}	83	85	4{*6,9*}	85	93
4{*4,2*}	85	89	4{*6,10*}	85	89
4{*4,4*}	87	83	4{*6,11*}	87	94
4{*4,5*}	83	86	4{*6,12*}	89	90
4{*4,6*}	84	89			

[a] Isolated yield. [b] Determined by HPLC analysis.

To the best of our knowledge, this new procedure provides the first example of a catalyst-free synthesis of spirooxindole-annulated indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidines. The catalyst-free reactions carried out in ethanol are considerably safer, nontoxic, environmentally friendly, and inexpensive. The absence of catalyst for the reaction avoids the use of moisture-sensitive and heavy-metal materials, such as Lewis acids. This method method is

Scheme 2. Synthesis of Spiroacenaphthylene-1,4′-indeno-1,5′-pyrido[2,3-*d*]pyrimidines 6



1 2{*1,2,5,6*} 5

Entry	Yield (%)	Purity (%)
6{*1*}	89	94
6{*2*}	85	92
6{*5*}	78	91
6{*6*}	82	>95

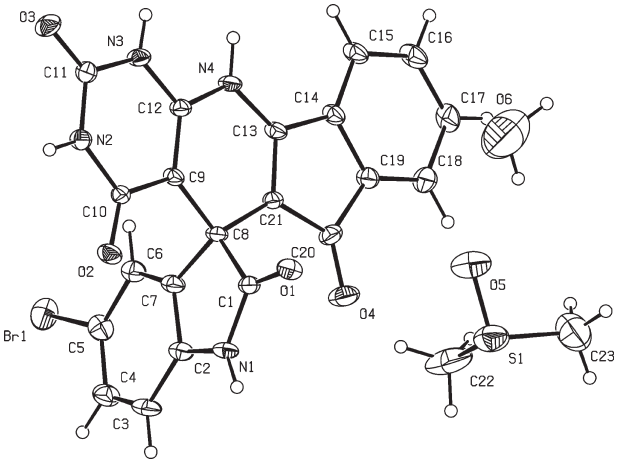


Figure 3. X-ray crystal structure of **4**{*1,5*}.

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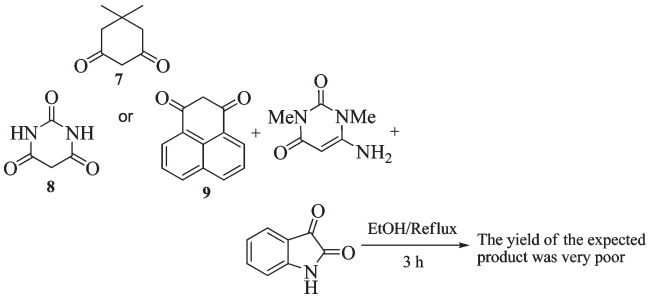
applicable for the synthesis of different types of spiroindeno[1,2-*b*]-pyrido[2,3-*d*]pyrimidine-5,3′-indolines. In addition, the workup of these very clean reactions involves only a filtration and simple washing step with ethanol and water. Using this simple purification protocol the desired products are obtained in good purity passed microanalysis.

We have not established an detailed mechanism for the formation of spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines **4**; however, a reasonable possibility is shown in Supporting Information.

As expected, when the isatin **3** was replaced by acenaphthylene-1,2-dione **5**, spiroacenaphthylene-1,4′-indeno-1,5′-pyrido[2,3-*d*]-pyrimidines **6** were obtained in good yields under the same reaction conditions (Scheme 2).

Scheme 3. Reaction of Other Cyclic Diketones



Compounds **4** and **6** are stable solids whose structures were established by IR, ^{1}H, and ^{13}C NMR spectroscopy and elemental analysis. The structure of **4**{*1,5*} was confirmed by a single-crystal X-ray analysis[15] (Figures 3).

It is notable that when the reaction of amino uracils **2**{*2*} and isatin **3**{*1*} was carried out with other cyclic diketones, such as dimedone **7**, barbituric acid **8**, and 1*H*-phenalene-1,3(2*H*)-dione **9** in the same conditions, TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products and the yield of the expected product was very poor (Scheme 3).

Finally, selected synthesized compounds were screened for antimicrobial activity. The microorganisms used in this study were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginusa* ATCC 85327, *Klebsiella pneumoniae* (Gram-negative bacteria), *Enterococcus faecalis* ATCC 29737, *Bacillus subtilis* ATCC 465, and *Staphylococcus aureus* ATCC 25923 (Gram-positive bacteria). The minimum inhibitory concentration (MIC) of the synthesized compounds determined by microdillution method[16] (Table 2). As can be seen from Table 2, good antibacterial activity was observed for most of the compounds against all species of Gram positive and Gram negative bacteria used in the study.

In conclusion, we have described a facile, catalyst-free three-component method for the synthesis of spiroindeno[1,2-*b*]pyrido-[2,3-*d*]pyrimidine-5,3′-indolines and spiroacenaphthylene-1,4′-indeno-1,5′-pyrido[2,3-*d*]pyrimidines in ethanol using readily available starting materials. The present procedure has many

Table 2. MIC (μg/mL) Values of Products 4 and 6

	microorganism					
product	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Enterococcus faecalis*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
4{*1,1*}	24	12	64	32	*a*	64
4{*1,2*}	32	24	24	64	*a*	32
4{*1,6*}	12	8	12	24	32	12
4{*2,2*}	4	*a*	*a*	32	128	*a*
4{*2,5*}	8	16	*a*	24	64	32
4{*2,6*}	8	8	*a*	12	24	16
4{*3,5*}	24	64	*a*	*a*	*a*	*a*
4{*3,6*}	16	32	*a*	*a*	128	*a*
4{*4,1*}	16	32	24	16	64	32
4{*4,2*}	*a*	64	16	16	*a*	256
4{*4,4*}	512	32	32	32	16	32
4{*4,5*}	2	2	8	8	8	32
4{*4,6*}	128	2	64	8	16	64
4{*5,2*}	*a*	16	16	64	*a*	*a*
4{*5,3*}	*a*	256	32	*a*	64	*a*
4{*5,6*}	*a*	128	64	64	64	*a*
4{*6,1*}	128	64	*a*	*a*	128	64
4{*6,4*}	128	*a*	*a*	*a*	256	64
4{*6,6*}	64	256	*a*	*a*	128	128
4{*6,10*}	64	32	*a*	128	64	64
4{*6,11*}	32	32	*a*	*a*	64	24
6{*1*}	64	*a*	256	*a*	*a*	512
6{*5*}	32	32	*a*	32	*a*	128
6{*6*}	64	16	16	4	32	32

[a] Not active.

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advantages, such as operational simplicity, good yields in short reaction times, and easy workup procedures.

EXPERIMENTAL PROCEDURES

General Procedure for Preparation of Spiroindeno[1,2-b]-pyrido[2,3-d]pyrimidine-5,3′-indolines 4. A mixture of 1,3-indandione (1 mmol), amino uracil (1 mmol), and isatin (1 mmol) in refluxing ethanol (5 mL) was stirred for 3 h. After completion of the reaction, progress of reaction was monitored using 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 product **4**.

ASSOCIATED CONTENT

Supporting Information. 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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(15) X-ray data for **4**{*1,5*}:($C_{21}H_{11}Br_1N_4O_4$)(DMSO, H_2O), M = 559.33 g/mol, triclinic system, space group $P\bar{1}$, a = 9.9246(17) Å, b = 11.6238(19) Å, c = 11.6546(18) Å, β = 104.096(13)°, V = 1154.4(3) Å^3, Z = 2, D_c = 1.609 g cm^{-3}, μ(Mo Kα)= 1.920 mm^{-1}, crystal dimention of 0.28 × 0.20 × 0.08 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs.[17] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0840, R_2 = 0.2454, and S = 1.098 with 330 parameters using 6211 independent reflection (θ range = 1.98−29.27°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **4**{*1,5*} have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 789416, Union Road, Cambridge CB2 1EZ, U.K. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

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