Recyclization in the Series of Spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-triones Prepared by a Three-Component Reaction of Isatins with (Thio)barbituric Acids and Electron-Rich Anilines

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Abstract: A ring–ring transformation in the series of spiro[indole-3,5′-pyrimido[4,5-b]quinoline]-2,2′,4′-trione derivatives prepared by a three-component reaction of (thio)barbituric acids, electron-rich aromatic amines, and isatins was observed.

Key words: multicomponent reaction, barbituric acids, aromatic amines, isatins, spiro[indole-3,5′-pyrimido[4,5-b]quinoline]-2,2′,4′-triones, recyclization

The heterocyclic oxindole system containing one carbon atom common to two rings is a widely distributed structural framework present in a number of pharmaceuticals and natural products.[1] The presence of the chiral spiro carbon leads to the sterically constrained spiro structure and is one of the important factors of the biological activities. Thus, the spirooxindole and spiroindoline ring systems are present in a number of natural alkaloids, including anesthetics (horsfiline),[2a] mammalian cell cycle inhibitors (spirotryprostatins A and B),[2b] and in synthetic drugs (for instance, ibutamoren mesylate, an orally active nonpeptide growth hormone secretagogue[3]) (Figure 1).

On the other hand, the target scaffold includes so important motifs such as 6-aminouracil and 1,4-dihydropyridine. The latter are known to be calcium agonists and calcium channel blockers (for example, nifedipine).[4] 6-(2-Aminoethyl)amino-5-chlorouracil (AEAC), which belongs to a class of 6-aminouracils, is a thymidine phosphorylase inhibitor and exhibits antitumor activity[5] (Figure 1). The combination of these moieties presents intriguing possibilities for pharmacological studies and drug design.

Multicomponent reactions (MCRs) as the synthetic approach to such scaffolds are very advantageous in many aspects. Such reactions offer a wide range of possibilities for the efficient construction of complex molecules in a single procedural step and are perfectly amenable to automation for combinatorial synthesis. Because of their convergence and productivity, the MCRs have attracted considerable attention from the point of view of combinatorial and medicinal chemistry and are particularly useful for the preparation of spiro heterocyclic systems.[6] Iaroshenko and co-workers[6h] have recently communicated a practical route to 7-azaindole framework by a one-pot, three-component cyclocondensation of N-substituted 2-amino-4-cyanopyrroles, various aldehydes, and active methylene compounds.

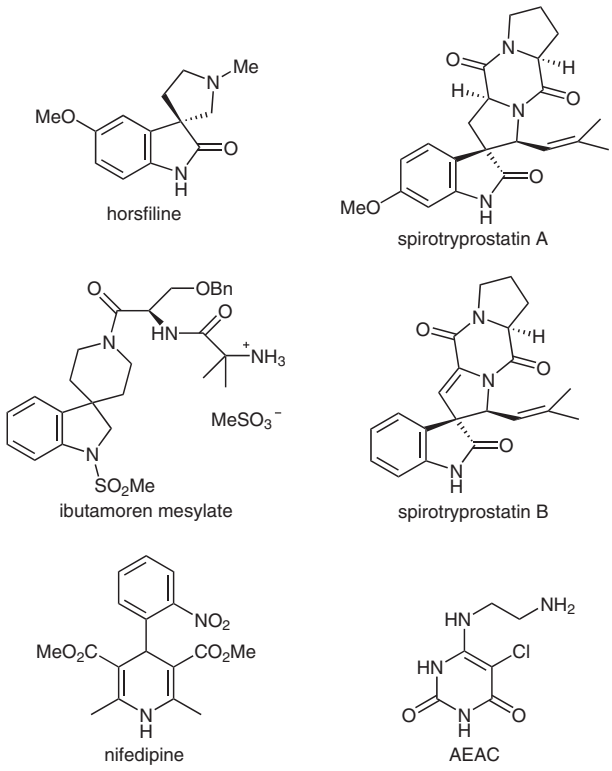

Figure 1 Representatives of important spiroindoles, 1,4-dihydropyridines, and 6-aminouracils

Continuing our research program[7] on the efficient synthesis of drug-like fused pyridines, we have undertaken attempts in the context of special interest in the synthesis of spiro heterocycles containing uracil, 1,4-dihydropyridine, and indole ring fragments by a three-component reaction of (thio)barbituric acids, aromatic amines, and isatins. We now report that such compounds can be obtained under mild reaction conditions in the presence of iodine. More-

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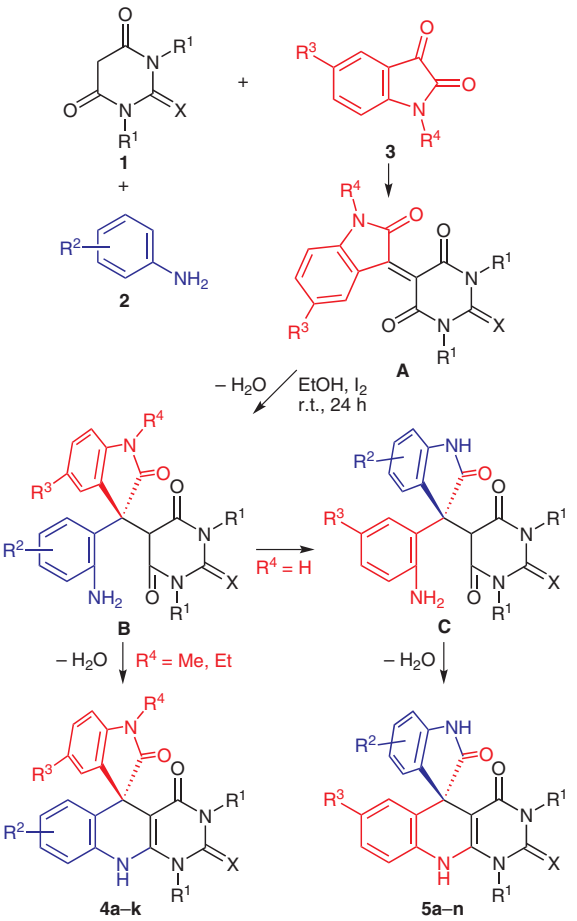
over, in the case of N-unsubstituted isatins, unexpected recyclization of spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-trione derivatives was observed.

Recently, there have been many reports on the synthesis of spiro[dihydropyridine-oxindole] compounds from isatins, 2-naphthylamine, and 1,3-dicarbonyls[8] as well as from isatins, heterocyclic amines, and barbituric acids[9] via the Hantzsch-like reaction in the presence of various catalysts and under various conditions. However, to the best of our knowledge, there are no literature data for the preparation of spiroindolinone derivatives from isatins, aromatic amines, and barbituric acids.[10]

We report now on the formation of spiro[indole-3,5′-pyrimido[4,5-b]quinoline]-2,2′,4′-triones from barbituric and thiobarbituric acids, electron-rich anilines, and N-substituted and N-unsubstituted isatins. Thus, four commercially available barbituric acid derivatives **1**, three electron-rich anilines **2**, and six isatins **3** were chosen for the library validation.

In the initial study, we have developed the synthesis of the hitherto unknown spiro heterocycles **4** starting from *N*-methyl- and *N*-ethylisatins by a one-pot, three-component reaction depicted in Scheme 1. Different catalysts and solvents were first briefly examined and the best result was obtained by using iodine as catalyst and EtOH as the solvent.[11] It was found that treatment of N-substituted isatins with dimethylbarbituric or diethylthiobarbituric acids and anilines (3,5-dimethoxy-, 3,4,5-trimethoxyanilines, 2-anthracenamine) in ethanol in the presence of a catalytic amount of iodine (0.05 equiv) at room temperature resulted in the formation of expected spiroindolinones **4a–i** in moderate to high yields (47–86%). In most cases, the reaction was complete after 24 hours and the products could be isolated by simple filtration of the precipitate formed. The progress of the reaction was monitored by TLC, and the results are summarized in Table 1. It is important that only electron-rich anilines **2** can effectively participate in the reaction with **1** and **3**, providing a variety of compounds **4** with high purity. The regiochemistry of **4c** and **4f** was confirmed by 2D NOESY experiments. Spiroindolinones **4** are likely formed via initial condensation of isatins **3** with barbituric acids **1** to afford the Knoevenagel product **A**,[12] which then undergoes in situ Michael addition with anilines **2** (these electron-rich compounds act as C-nucleophiles) followed by the cyclocondensation of the intermediate **B** to give the corresponding products **4** (Scheme 1).

To expand the scope of the present reaction, isatin and its 5-substituted derivatives were examined to replace *N*-methyl- and *N*-ethylisatins. However, when the three-component reaction of N-unsubstituted isatins, electron-rich anilines and (thio)barbituric acids was conducted under the same condition (ethanol, I_2, r.t., 24 h), isomeric spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-trione



Scheme 1 Synthesis of isomeric spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-triones **4** and **5** by a three-component reaction

derivatives **5a–l** were obtained in variable 26–91% yields (Table 1). Their spectral data were similar but inconsistent with the expected structure **4**. Indeed, the data were in good agreement with the structure of an unexpected product **5**, being constructed via ring-opening of N-unsubstituted spiroindolinone fragment followed by formation of a dihydropyridine ring from intermediate **C**. Selected NMR spectral data of isomers **4** and **5** (Figure 2) are summarized in Tables 2–5. It should be also noted that singlets for the dihydropyridine proton H-10′ in **4** and **5** appeared at δ = 9.16–9.22 and 9.14–9.59, respectively. To confirm the conclusion about the regiochemistry of **5**, additional 2D NOESY experiment was carried out for **5c** (see SI), which exhibits strong cross-peaks between protons H-1 and H-7 as well as between H-10′ and H-9′, and H-10′ and CH_3-1′, indicating that they are spatially close to each other (Figure 3). Moreover, the structures of compounds **5b** (Figure 4) and **5f** (Figure 5) were unambiguously confirmed by X-ray single crystal analysis. Recently, similar transformation of the indolinone ring have been observed in the reaction of 6-aminouracils with isatins.[13]

Table 1 Isomeric Spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-triones **4a–k** and **5a–n**

Barbituric acid **1**		Aniline **2**	Isatin **3**		Products **4** and **5**	
R^1	X	R^2	R^3	R^4	Isomer	Yield (%)[a]
Me	O	3,5-$(MeO)_2$	H	Me	**4a**	86
Me	O	3,4,5-$(MeO)_3$	H	Me	**4b**	52
Me	O	3,5-$(MeO)_2$	H	Et	**4c**	82
Me	O	3,4,5-$(MeO)_3$	H	Et	**4d**	55
Et	S	3,5-$(MeO)_2$	H	Me	**4e**	56
Et	S	3,4,5-$(MeO)_3$	H	Me	**4f**	47
Et	S	3,5-$(MeO)_2$	H	Et	**4g**	72
Et	S	3,4,5-$(MeO)_3$	H	Et	**4h**	47
Et	S	2-anthraceneamine	H	Et	**4i**	73
H	O	3,5-$(MeO)_2$	H	H	**5a**	51
Me	O	3,5-$(MeO)_2$	H	H	**5b**	57
Me	O	3,5-$(MeO)_2$	Cl	H	**5c**	72
Me	O	3,5-$(MeO)_2$	F	H	**5d**	75
Pr	O	3,5-$(MeO)_2$	H	H	**5e**	79
Pr	O	3,4,5-$(MeO)_3$	H	H	**5f**	26
Pr	O	2-anthraceneamine	H	H	**5g**	91
Et	S	3,5-$(MeO)_2$	H	H	**5h**	81
Et	S	3,4,5-$(MeO)_3$	H	H	**5i**	53
Et	S	3,5-$(MeO)_2$	Cl	H	**5j**	68
Et	S	3,5-$(MeO)_2$	F	H	**5k**	59
Et	S	3,4,5-$(MeO)_3$	F	H	**5l**	36
Me	O	3,4,5-$(MeO)_3$	NO_2	H	**4j** + **5m** (85:15)	67/23[b]
Et	S	3,5-$(MeO)_2$	NO_2	H	**4k** + **5n** (25:75)	63/19[b]

[a] Yields refer to pure isolated products.
[b] Yield of isolated mixture/yield of the major isomer isolated in a pure state.

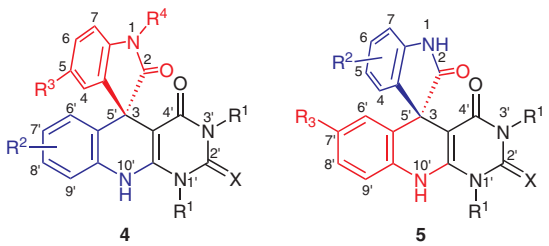


Figure 2 Isomers **4** and **5**

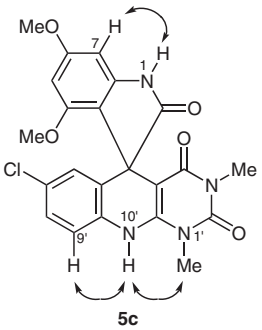


Figure 3 Determination of regioisomer **5c** by 2D NOESY (for the original 2D NOESY spectra, see the Supporting Information); arrows show the decisive correlations

Table 2 The ^{1}H and ^{13}C NMR Data for Isomers **4** from 3,5-Dimethoxyaniline

Isomer **4**	^{1}H NMR, δ				^{13}C NMR, δ			
	CH_3O-6′	CH_3O-8′	H-7′	H-9′	CH_3O-6′	CH_3O-8′	CH-7′	CH-9′
4a	3.36	3.77	6.12	6.67	56.8	56.1	95.5	95.0
4c	3.32	3.77	6.13	6.67	56.9	57.4	97.8	97.4
4e	3.38	3.78	6.15	6.79	56.9	56.2	96.0	95.2
4g	3.34	3.79	6.16	6.80				

Table 3 The ^{1}H and ^{13}C NMR Data for Isomers **5** from 3,5-Dimethoxyaniline

Isomer **5**	^{1}H NMR, δ				^{13}C NMR, δ			
	CH_3O-4	CH_3O-6	H-5	H-7	CH_3O-4	CH_3O-6	CH-5	CH-7
5b	3.50	3.76	6.04	6.12				
5c	3.53	3.77	6.07	6.14	56.5	56.2	93.1	90.2
5d	3.52	3.77	6.07	6.13	56.5	56.2	93.1	90.2
5e	3.49	3.75	6.03	6.11	56.4	56.1	92.9	90.1
5h	3.51	3.76	6.05	6.13	56.5	56.2	93.1	90.2
5j	3.54	3.77	6.09	6.15	56.6	56.2	93.2	90.3
5k	3.53	3.77	6.08	6.15	56.5	56.2	93.2	90.3
5n	3.54	3.78	6.10	6.20	56.6	56.2	93.3	90.4

Table 4 The ^{1}H and ^{13}C NMR Data for Isomers **4** from 3,4,5-Trimethoxyaniline

Isomer **4**	^{1}H NMR, δ				^{13}C NMR, δ			
	CH_3O-6′	CH_3O-7′	CH_3O-8′	H-9′	CH_3O-6′	CH_3O-7′	CH_3O-8′	CH-9′
4b	3.12	3.60	3.83	6.93	60.4	61.2	56.6	97.2
4d	3.03	3.60	3.83	6.92	60.1	61.1	56.6	97.2
4f	3.14	3.61	3.85	6.97	60.4	61.2	56.7	97.5
4h	3.04	3.61	3.85	7.05	60.2	61.1	56.7	97.5
4j	3.27	3.62	3.85	6.96	60.4	61.2	56.7	97.3

Table 5 The ^{1}H and ^{13}C NMR Data for Isomers **5** from 3,4,5-Trimethoxyaniline

Isomer **5**	^{1}H NMR, δ				^{13}C NMR, δ			
	CH_3O	CH_3O	CH_3O	H-7	CH_3O	CH_3O	CH_3O	CH-7
5f	3.29	3.59	3.83	6.36	56.8	60.8	61.3	92.0
5i	3.28	3.59	3.83	6.38	56.9	60.8	61.4	92.1
5l	3.33	3.61	3.84	6.40	56.9	60.9	61.4	92.2

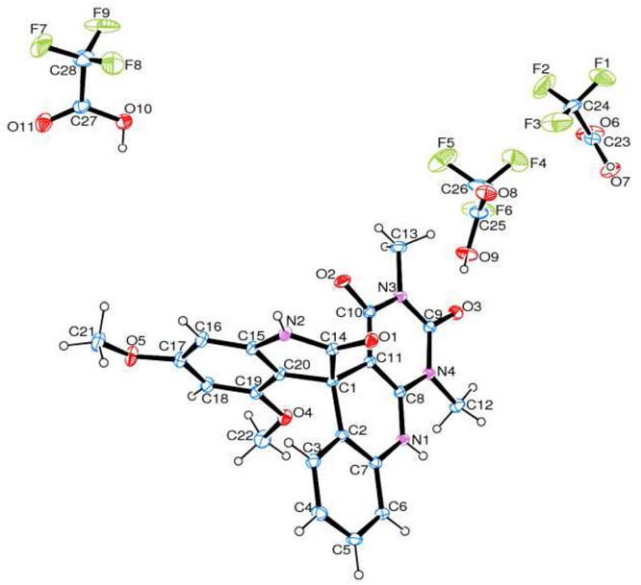


Figure 4 ORTEP plot of 4,6-dimethoxy-1′,3′-dimethyl-1′*H*-spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′(1*H*,3′*H*,10′*H*)-trione (**5b**) (thermal ellipsoids at 50% probability)

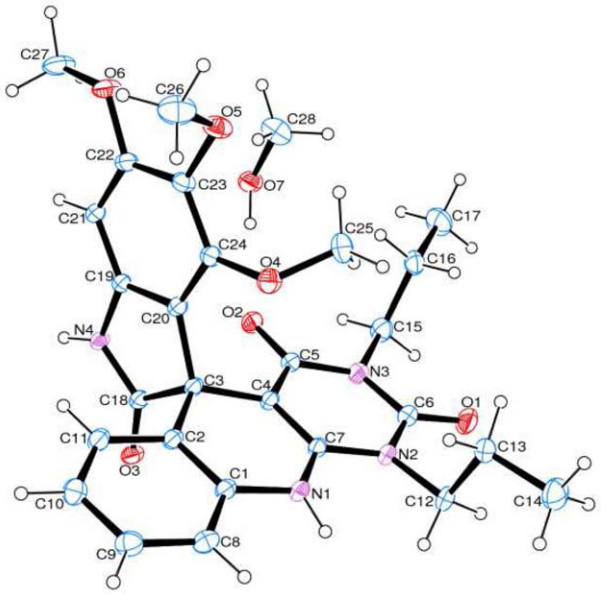


Figure 5 ORTEP plot of 4,5,6-trimethoxy-1′,3′-dipropyl-1′*H*-spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′(1*H*,3′*H*,10′*H*)-trione (**5f**) (thermal ellipsoids at 50% probability)

As can be seen from Table 1, the reaction described has virtually no limitations as regards the length of the alkyl substituent in the (thio)barbituric molecule, but requires N-unsubstituted isatins. This result and the absence of the isomeric products **4** seem to indicate that the N-unsubstituted isatin fragment facilitates the rearrangement of intermediate **A** into **B** toward formation of the thermodynamically favored amide bond in spiroindolinone moiety **5** (Scheme 1). Only in the case of 5-nitroisatin the mixtures **4j** + **5m** = 85:15 and **4k** + **5n** = 25:75 were obtained, from which major isomers **4j** and **5n** were isolated in a pure state (Table 1).

Next, attempts were made to replace isatins by other active carbonyl compounds, such as chloral hydrate and ethyl pyruvate. When chloral hydrate was subjected to an analogous reaction, the unexpected product **6** with a hydrolyzed trichloromethyl group from the four-component reaction was obtained under the same conditions in 17% yield. Fused 1,4-dihydropyridine **7**, prepared from ethyl pyruvate in 25% yield, is an unstable product and rearranges slowly at room temperature under the action of atmospheric moisture to give quantitatively indolinone **8** (Scheme 2). The structures of compounds **6**–**8** were characterized by IR, ^{1}H, ^{13}C NMR spectral data as well as MS and HRMS analyses. In addition, the structure of **8** is confirmed by X-ray diffraction analysis (Figure 6).[14]

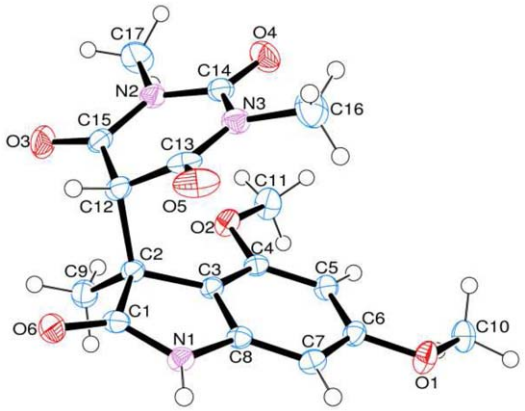
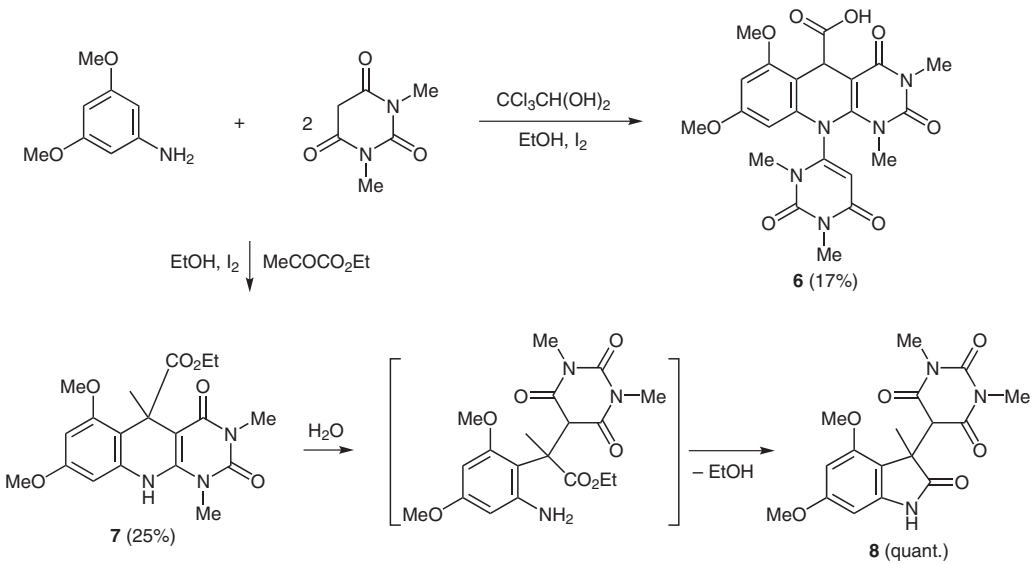


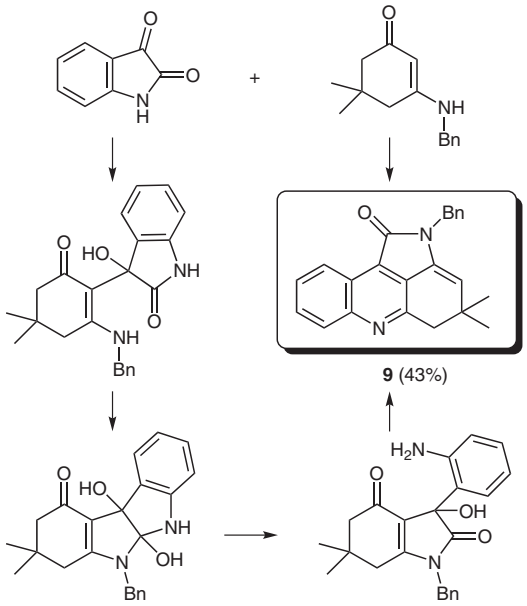
Figure 6 ORTEP plot of 5-(4,6-dimethoxy-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**8**) (thermal ellipsoids at 50% probability)

Treatment of isatin with 3-benzylamino-5,5-dimethylcyclohex-2-enone resulted in the formation of 2-benzyl-4,4-dimethyl-4,5-dihydropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (**9**) in 43% yield (Scheme 3). Very recently, this reaction has been described for the three-component condensation of isatin, dimedone, and various amines.[15]

In conclusion, we have developed a novel and efficient synthesis of spiroindolinones via a three-component reaction between (thio)barbituric acids, electron-rich anilines, and isatins. The described synthesis in ethanol media in the presence of iodine is a simple, practical, and environmentally friendly method for the preparation of heterocyclic compounds containing spiroindole-3,5′-pyrimido[4,5-*b*]quinoline system, which undergoes an unexpected recyclization related with the indolinone ring opening in the case of N-unsubstituted isatins. On the other hand, the combinatorial aspect of the developed here synthetic strategies can be used in the biology-oriented syntheses; this investigations have already been started.



Scheme 2 Synthesis of compounds **6**–**8**



Scheme 3 Synthesis of compound **9**

All solvents were purified and dried by standard methods. NMR spectra were recorded on a Bruker AV 300 and Bruker AV 400. IR spectra were recorded on a PerkinElmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained using a Hewlett-Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F254 plates were used for TLC analysis. Chemical yields refer to pure isolated substances.

Spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′-triones 4 and 5; General Procedure

Into a 25 mL flask were placed the corresponding barbituric acid **1** (1.92 mmol), isatin **3** (1.92 mmol), aromatic amine **2** (1.92 mmol), and EtOH (6 mL). I_2 (0.096 mmol, 0.05 equiv) was then added and the mixture was stirred overnight at r.t. The next day, the precipitate that had formed was collected by filtration, washed with EtOH (2 × 3 mL), and recrystallized from an appropriate solvent, if necessary.

6′,8′-Dimethoxy-1,1′,3′-trimethyl-1′*H*-spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′ (1*H*,3′*H*,10′*H*)-trione (4a)

Yield: 716 mg (86%); white solid; mp >320 °C.

^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 3.01 (s, 3 H, NCH_3-3′), 3.20 (s, 3 H, NCH_3-1), 3.36 (s, 3 H, CH_3O-6′), 3.55 (s, 3 H, NCH_3-1′), 3.77 (s, 3 H, CH_3O-8′), 6.12 (d, ^4J = 2.6 Hz, 1 H, H-7′), 6.67 (d, ^4J = 2.6 Hz, 1 H, H-9′), 6.77–6.85 (m, 1 H, H-5), 6.85 (d, ^3J = 7.2 Hz, 1 H, H-4), 6.88 (d, ^3J = 7.7 Hz, 1 H, H-7), 7.13–7.20 (m, 1 H, H-6), 9.17 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 27.1 (NCH_3-1), 28.3 (NCH_3-3′), 31.1 (NCH_3-1′), 49.6 (C-3,5′), 56.1 (CH_3O-8′), 56.8 (CH_3O-6′), 87.2 (C-4a′), 95.0 (CH-9′), 95.5 (CH-7′), 105.2, 107.4 (CH_{Ar}), 122.2 (CH_{Ar}), 123.7 (CH_{Ar}), 128.2 (CH_{Ar}), 136.8, 138.1, 145.6, 146.2, 151.2, 159.1, 160.1, 160.6, 179.8 (C=O-2).

MS (EI, 70 eV): *m*/*z* (%) = 435 ([M + H]$^+$, 14), 434 ([M]$^+$, 59), 406 (18), 376 (34), 375 (100), 318 (11), 44 (16).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{22}N_4O_5$ [M]$^+$: 434.15847; found: 434.15903.

7′-Chloro-4,6-dimethoxy-1′,3′-dimethyl-1′*H*-spiro[indole-3,5′-pyrimido[4,5-*b*]quinoline]-2,2′,4′ (1*H*,3′*H*,10′*H*)-trione (5c)

Yield: 627 mg (72%); white solid; mp >320 °C.

^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 3.08 (s, 3 H, NCH_3-3′), 3.53 (s, 3 H, CH_3O-4), 3.56 (s, 3 H, NCH_3-1′), 3.77 (s, 3 H, CH_3O-6), 6.07 (d, ^4J = 2.1 Hz, 1 H, H-5), 6.14 (d, ^4J = 2.1 Hz, 1 H, H-7), 6.59 (d, ^4J = 2.5 Hz, 1 H, H-6′), 7.26 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1 H, H-8′), 7.34 (d, ^3J = 8.7 Hz, 1 H, H-9′), 9.45 (br s, 1 H, NH-10′), 10.45 (br s, 1 H, NH-1).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.3 (NCH_3-3′), 31.0 (NCH_3-1′), 51.0 (C-3,5′), 56.2 (CH_3O-6), 56.5 (CH_3O-4), 84.6 (C-4a′), 90.2 (CH-7), 93.1 (CH-5), 117.3, 119.4 (CH-9′), 125.0 (C-5a′), 125.9 (CH-6′), 127.5, 128.7 (CH-8′), 135.9 (C-9a′), 143.7, 146.7, 151.3, 156.8, 160.3, 161.8, 181.3 (C=O-2).

MS (GC, 70 eV): *m*/*z* (%) = 454 ([M]$^+$, ^{35}Cl, 35), 453 (27), 452 (100), 423 (14), 421 (39), 412 (21), 411 (15), 410 (57), 290 (19), 289 (10), 288 (51).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{20}{}^{35}ClN_4O_5$ $[M + H]^+$: 455.11167; found: 455.11218.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedures, characterization data, and ^1H, ^{13}C NMR spectra of all compounds.

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(14) Crystallographic data (excluding structure factors) for the structures **5b**, **5f**, and **8** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 921314–921316 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.

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