Three-component condensation of 5-aminopyrazole derivatives with isatins and Meldrum´s acid. Synthesis of 1,7-dihydrospiro[pyrazolo[3,4-*b*]-pyridine-4,3´-indole]-2´,6(1´*H*,5*H*)-diones

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A new method for the synthesis of hitherto unknown substituted 1,7-dihydrospiro-[pyrazolo[3,4-*b*]pyridine-4,3´-indole]-2´,6(1´*H*,5*H*)-diones based on three-component condensation of 5-aminopyrazoles with Meldrum´s acid and isatins is developed.

Key words: isatins, three-component condensation, Meldrum´s acid, 5-aminopyrazoles, decarboxylation, 1,7-dihydrospiro[pyrazole[3,4-*b*]pyridine-4,3´-indole]-2´,6(1´*H*,5*H*)-diones.

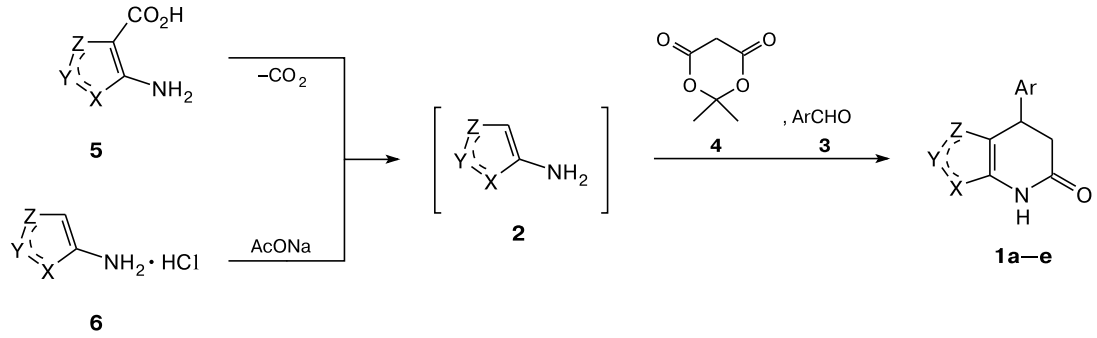
Earlier,[1—6] we have developed a general method for the synthesis of fused systems **1** containing a dihydropyridinone residue based on a three-component condensation of labile heterocyclic amines **2** with aldehydes **3** and Meldrum´s acid **4** (Scheme 1).

Undoubtedly, the advantage of this method is the possibility of production of unstable aminoheterocycles *in situ* from vicinal aminocarboxylic acids **5**, which are formed upon alkaline hydrolysis of the corresponding easily accesible esters[1,2,4] or as the result of neutralization of stable hydrochlorides **6** with anhydrous sodium acetate.[3,5,6] It is of note that it is aromatic aldehydes that have been used in this condensation. At the same time, it is obvious that the extending of the panel of the aldehydes that can be used in the described process as well as the use of ketones will allow significant diversification of the structures of this three-component condensation products.

We anticipated that isatins can be aromatic aldehyde analogs, which will result in fused spirosystems containing an indolone fragment. The synthesis of spirooxyindole systems based on the condensation of isatins with dimedone[7] and substituted 6-aminouracils,[8] resulting in spiro-[indoline-3,9´-xantene]trione and spiro[pyrimido[4,5-*b*]-quinoline-5,5´-pyrrolo[2,3-*d*]pyrimidine]pentone derivatives, respectively, have been described. It is worth mentioning that the spirooxyindole system is the key structural fragment of many biologically active compounds and natural alkaloids.[9—12]

The aim of the present work was to synthesize hitherto unknown substituted 1,7-dihydrospiro[pyrazolo[3,4-*b*]-

Scheme 1



	1a	1b	1c	1d	1e
X	S	N	CR^1	N	CR^1
Y	CR^1	CR^1	CR^2	CR^1	N
Z	CR^2	S	S	Se	S

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pyridine-4,3′-indole]-2′,6(1′*H*,5*H*)-diones **7** based on a three-component condensation of 5-aminopyrazole derivatives **8**, isatins **9**, and Meldrum′s acid **4** (Scheme 2). We demonstrated that the reaction of compounds **4**, **8**, and **9** leads to compounds **7** in good yields. Acids **10** necessary for the synthesis of compounds **7** readily undergo decarboxylation[13] leading to 5-aminopyrazoles **8**, and can be obtained as sodium salts by alkaline hydrolysis[14] of the corresponding esters **12**.

5-Aminopyrazoles **8** are stable compounds, which can be obtained in the free form from esters **12** in two steps.[13] In our case, amines **8** were generated *in situ* from preformed sodium salts **11a—c**. The latter were obtained upon alkaline hydrolysis of esters **12a—c** and were used in the three-component condensation without additional purification.

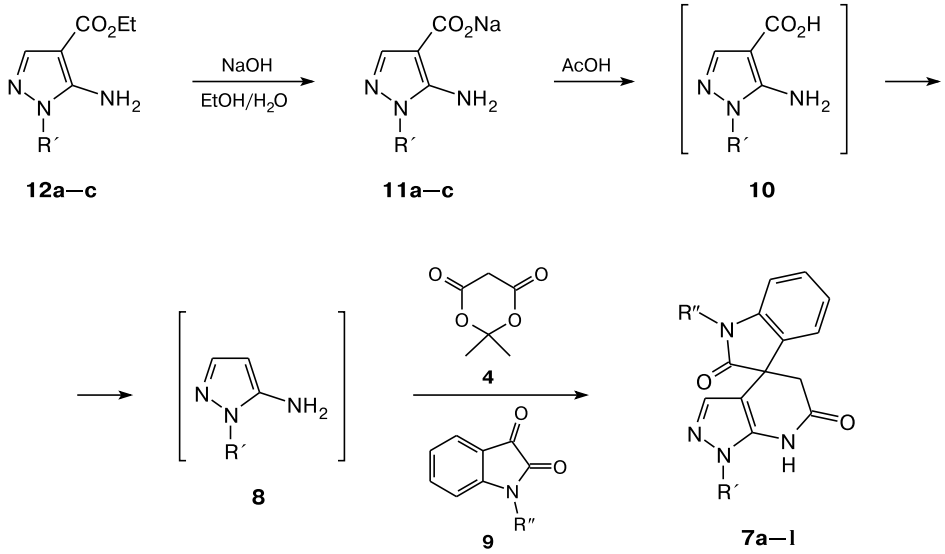
We assume that the reaction occurs according to one of two most probable paths (Scheme 3). Thus, isatin can first add to 5-aminopyrazole **8** giving the adduct **13**, which further reacts with Meldrum′s acid to form unstable intermediate **14**, which eliminates CO_2 and acetone (path *A*) affording the final product **7**. An alternative scheme of the process includes the Michael addition of 5-aminopyrazole **8** to oxoindolylidene derivative of Meldrum′s acid **15** followed by the intermolecular cyclization (path *B*).

An important feature of the reaction investigated should be mentioned. In contrast to the previously described methods where aromatic aldehydes have been employed, we failed to isolate stable oxoindolylidene derivative **15** in the condensation of Meldrum′s acid with isatin. Thus, the approaches that have previously been applied for the arylidene derivatives of Medrum′s acid and stable heterocyclic enamines[15—17] are not suitable in this case. The synthesis of the target compounds **7** can be performed only under conditions of the three-component condensation of 5-aminopyrazole derivatives **8**, isatins **9**, and Meldrum′s acid **4**.

The obtained compounds are solid crystalline substances; their structures were confirmed by elemental analysis and data from ^{1}H NMR spectroscopy (Tables 1, 2). Characteristic doublets of the non-equivalent protons of the methylene unit at δ 2.42—3.19 are observed in the ^{1}H NMR spectra of the obtained products.

Thus, we developed a novel useful method of synthesis of hitherto unknown substituted 1,7-dihydrospiro[pyrazolo[3,4-*b*]pyridine-4,3′-indole]-2′,6(1′*H*,5*H*)-diones based on the three-component condensation of 5-aminopyrazoles, Meldrum′s acid, and isatins. It was found that sodium 5-aminopyrazole-4-carboxylates can act as synthetic equivalents of 5-aminopyrazoles. It was demonstrated that the reaction can be performed only as the

Scheme 2



11, 12: R′ = H (**a**), Ph (**b**), CMe_3 (**c**)

Compound	R′	R″	Compound	R′	R″	Compound	R′	R″
7a	H	H	**7e**	H	$H_2C—C≡CH$	**7i**	Ph	$PhCH_2$
7b	H	Me	**7f**	H	$PhCH_2$	**7j**	CMe_3	H
7c	H	Et	**7g**	Ph	$H_2C—CH=CH_2$	**7k**	CMe_3	Me
7d	H	$H_2C—CH=CH_2$	**7h**	Ph	$H_2C—C≡CH$	**7l**	CMe_3	$H_2C—C≡CH$

Scheme 3

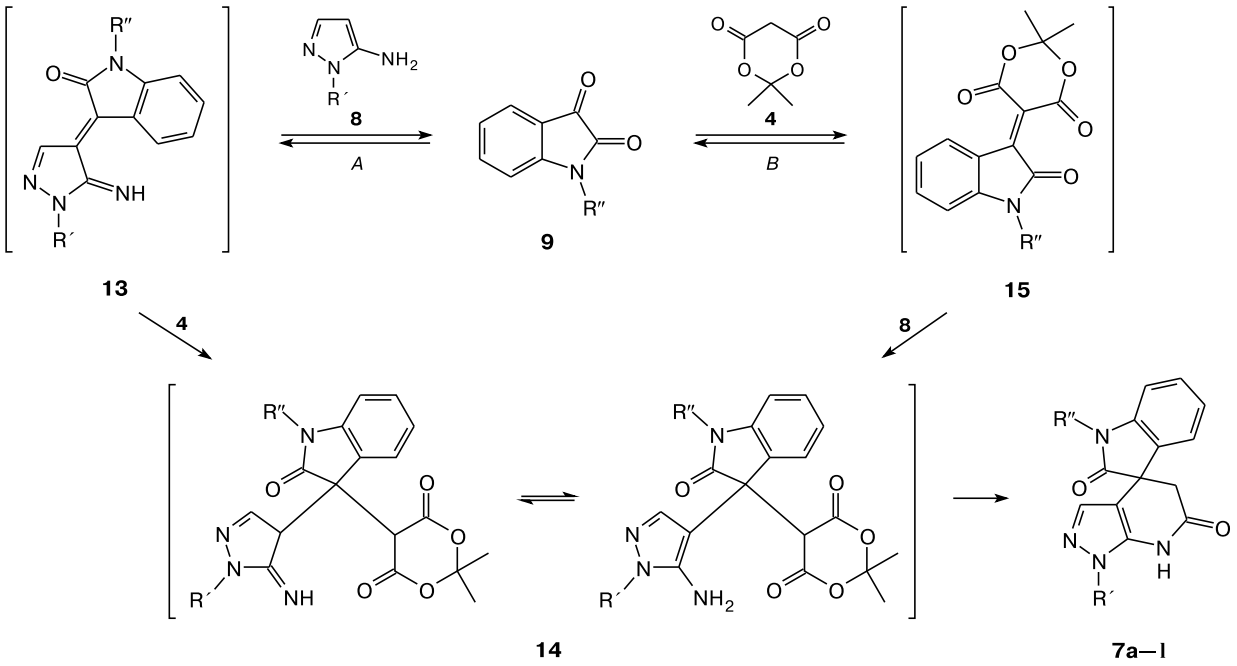


Table 1. Yields, melting points, and elemental analysis data for compounds **7a—l**

Compound	Substituents		M.p. /°C	Yield (%)	Found / Calculated (%)			Molecular formula
	R′	R″			C	H	N	
7a	H	H	>300 decomp.	60	61.71 61.41	3.89 3.96	22.18 22.04	$C_{13}H_{10}N_4O_2$
7b	H	Me	>300 decomp.	50	62.49 62.68	4.60 4.51	21.04 20.88	$C_{14}H_{12}N_4O_2$
7c	H	Et	261—262	51	64.01 63.82	4.93 5.00	20.01 19.85	$C_{15}H_{14}N_4O_2$
7d	H	H_2C—CH=CH_2	>300	59	65.11 65.30	4.86 4.79	19.15 19.04	$C_{16}H_{14}N_4O_2$
7e	H	H_2C—C≡CH	297—298	54	65.58 65.75	4.07 4.14	19.30 19.17	$C_{16}H_{12}N_4O_2$
7f	H	$PhCH_2$	169—170	60	69.95 69.76	4.77 4.68	16.42 16.27	$C_{20}H_{16}N_4O_2$
7g	Ph	H_2C—CH=CH_2	149—151	65	71.52 71.34	4.98 4.90	15.29 15.13	$C_{22}H_{18}N_4O_2$
7h	Ph	H_2C—C≡CH	147—149	57	71.52 71.73	4.30 4.38	15.35 15.21	$C_{22}H_{16}N_4O_2$
7i	Ph	$PhCH_2$	129—130	71	74.45 74.27	4.69 4.79	13.21 13.32	$C_{26}H_{20}N_4O_2$
7j	CMe_3	H	>270 decomp.	72	65.94 65.79	5.79 5.85	18.16 18.05	$C_{17}H_{18}N_4O_2$
7k	CMe_3	Me	205—207	65	66.39 66.65	6.30 6.21	17.39 17.27	$C_{18}H_{20}N_4O_2$
7l	CMe_3	H_2C—C≡CH	211—212	78	67.12 68.95	5.70 5.79	16.21 16.08	$C_{20}H_{20}N_4O_2$

Table 2. ^{1}H NMR spectra for compounds **7a—l** (DMSO-d_6, δ, *J*/Hz)

Compound	R′	R″	H—C—H (d, 1 H, *J* = 16)	H—C—H (d, 1 H, *J* = 16)	Ar_{isatin}	$CH_{pyrazol}$	NH (br.s, 1 H)
7a	12.18 (br.s, 1 H)	10.53 (br.s, 1 H, NH)	2.84	2.49	6.88—7.26 (m, 5 H)		10.47
7b	12.19 (br.s, 1 H)	3.13 (s, 3 H, Me)	2.89	2.45*	7.04—7.36 (m, 5 H)		10.56
7c	12.19 (br.s, 1 H)	1.15 (t, 3 H, Me, *J* = 7); 3.68 (q, 2 H, CH_2, *J* = 7)	2.89	2.45	7.05—7.35 (m, 5 H)		10.55
7d	12.21 (br.s, 1 H)	4.29 (s, 2 H, CH_2); 5.13 (m, 2 H, CH_2); 5.87 (m, 1 H, CH)	2.95	2.48	6.98—7.32 (m, 5 H)		10.57
7e	12.23 (br.s, 1 H)	3.36 (s, 1 H, CH); 4.50 (s, 2 H, CH_2)	2.97	2.42	7.08—7.39 (m, 4 H)	7.02 (s, 1 H)	10.58
7f	12.23 (br.s, 1 H))	4.88 (s, 2 H, CH_2); 6.93—7.36 (m, 10 H, Ph)	2.99	2.52	6.93—7.36 (m, 10 H)		10.60
7g	7.03—7.55 (m, 5 H, Ph)	4.32 (s, 2 H, CH_2); 5.16 (m, 2 H, CH_2); 5.88 (m, 1 H, CH)	3.16	2.63	7.03—7.55 (m, 4 H)	6.97 (s, 1 H)	10.86
7h	7.12—7.57 (m, 5 H, Ph)	3.31 (s, 1 H, CH); 4.54 (s, 2 H, CH_2)	3.18	2.57	7.12—7.57 (m, 4 H)	6.93 (s, 1 H)	10.87
7i	6.99—7.59 (m, 5 H, Ph)	4.93 (s, 2 H, CH_2); 6.99—7.59 (m, 5 H, Ph)	3.19	2.67	6.99—7.59 (m, 4 H)	6.98 (s, 1 H)	10.90
7j	1.56 (s, 9 H, CMe)	10.48 (br.s, 1 H, NH)	2.95	2.51	6.86—7.26 (m, 4 H)	6.62 (s, 1 H)	10.33
7k	1.56 (s, 9 H, CMe_3)	3.13 (s, 3 H, Me)	2.99	2.51	7.04—7.37 (m, 4 H)	6.58 (s, 1 H)	10.37
7l	1.56 (s, 9 H, CMe_3)	3.28 (s, 1 H, CH); 4.51 (s, 2 H, CH_2)	3.07	2.48	7.09—7.40 (m, 4 H)	6.56 (s, 1 H)	10.42

* *J* = 16.7 Hz.

three-component process because of the instability of the oxoindolylidene derivatives of Meldrum´s acid.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker Avance II 300 spectrometer (300.00 MHz) in DMSO-d_6. The melting points were determined on a Boetius hot-stage apparatus and are uncorrected. The course of reactions and the purity of the obtained compounds were monitored by TLC (Silica gel 60 F254 (Merck), ethyl acetate—hexane, 3 : 1).

Synthesis of the starting esters[18,19] and alkylisatin derivatives[20—22] was carried out according to the described methods.

Synthesis of 1,7-dihydrospiro[pyrazolo[3,4-*b*]pyridine-4,3´-indole]-2´,6(1´*H*,5*H*)-diones (7a—l). A mixture of ester **12** (2 mmol) and NaOH (0.16 g, 4 mmol) in ethanol (5 mL) and water (5 mL) was refluxed for 4 h and concentrated to dryness. Meldrum´s acid (0.32 g, 2.3 mmol), the corresponding isatin (2.15 mmol), and acetic acid (7 mL) were added to the residue. The obtained mixture was refluxed for 6 h. Subsequent work-up of the reaction mixture was carried out according to one of the methods mentioned below.

Synthesis of compounds 7a—f (method *A*). The reaction mixture was concentrated *in vacuo*, water (5 mL) was added to the residue. The precipitate that formed was filtered off and recrystalized from acetone.

Synthesis of compounds 7g,h,l (method *B*). The reaction mixture was poured in water (100 mL), the precipitate that formed was filtered off and recrystalized from diethyl ether.

Synthesis of compounds 7i—k (method *C*). The reaction mixture was concentrated *in vacuo*, the residue was recrystallized from ethanol, filtered off, and washed with ethanol and water.

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