A new convenient four-component synthesis of 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitriles and one-pot synthesis of 6′-amino-5′-cyano-1,2-dihydrospiro-[(3*H*)-indole-3,4′-(4′*H*)-pyrano[2,3-*c*]pyrazol]-2-ones

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A new convenient method for the synthesis of 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitriles, namely, four-component condensation of carbonyl compounds (aromatic aldehydes, heterocyclic ketones), malononitrile, β-keto esters, and hydrazine hydrate in ethanol in the presence of triethylamine as a catalyst, which occurs selectively, is developed. One-pot two-step modification of this method is proposed for the synthesis of spiro[(3*H*)-indole-3,4′-(4′*H*)-pyrano[2,3-*c*]pyrazol]-2-ones.

Key words: four-component reaction, one-pot modification, 6-amino-2*H*,4*H*-pyrano-[2,3-*c*]pyrazole-5-carbonitriles, 2′-amino-5′-cyanospiro[(3*H*)-indole-3,4′-(4′*H*)-pyran]-2-ones, aromatic aldehydes, piperidin-4-ones, isatins, malononitrile, β-keto esters, hydrazine hydrate, triethylamine.

6-Aminopyrano[2,3-*c*]pyrazole-5-carbonitriles are the subject of extensive investigations.[1—12] The first example of the synthesis of these compounds was based on the reaction of tetracyanoethylene with 3-methylpyrazolin-5-one resulting in 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-4,4,5-tricarbonitriles.[1] 4-Aryl-[1—6] and 4-alkyl substituted pyranopyrazoles,[7,8] as well as heterocycles that contain spiro-fused rings[8—14] are among the well-known compounds of this class. 6-Amino-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole-5-carbonitrile was used in the synthesis of annulated heterocycles.[15] Some 6-aminopyrano-[2,3-*c*]pyrazole-5-carbonitriles demonstrate analgesic activity;[16] they were tested as potential inhibitors of human kinase Chk1 (*in vitro* and computer simulation).[17] Three-component condensation of aromatic aldehydes, malononitrile, and pyrazolin-5-ones[2,3,5,7,8,10—12] or step-by-step assembly methods with the isolation of arylidene-malononitriles[3,4] or 3-alkyl-4-arylidenepyrazolin-5-ones[6] are the standard methods for the synthesis of these heterocycles. Pyrano[2,3-*c*]pyrazoles are the only reaction products regardless of the order of addition of the reactants and the steps. Pyrazolin-5-ones, in turn, are obtained from β-keto esters and hydrazine hydrate.[18] Recently,[19,20] we have developed a four-component procedure for the synthesis of 3-alkyl-6-amino-4-arylpyrano[2,3-*c*]pyrazoles based on the reaction of aromatic aldehydes, malononitrile, β-keto esters, and hydrazine hydrate in ethanol in the presence of triethylamine.

All four components were dissolved in ethanol and the reaction was carried out by refluxing the reaction mixture for 15 min in the presence of triethylamine as the basic catalyst (method *A*). In principle, all four components may be varied in this multicomponent condensation: aromatic aldehydes **1a—k**, malononitrile **2**, β-keto esters **3a—d**, hydrazine hydrate **4**. Thus, the use of aromatic aldehydes with electron-withdrawing (**1b—e**) or electron-donating substituents (**1f—i**), and heterocyclic aldehydes **1j,k** results in products **5a—l** in 56—72% yields (Scheme 1). Variations of β-keto esters **3a—d** are also possible. However, ethyl pivaloylacetate (R^2 = Bu^t) did not give pyrano[2,3-*c*]pyrazole under analogous conditions even when the duration of the reaction was increased (up to 30—60 min), apparently, for steric reasons. Possibly, β-keto esters **3** and hydrazine hydrate **4** give pyrazolinones,[18] and aromatic aldehydes **1** undergo the Knoevenagel reaction with malononitrile **2** to give arylidenemalononitriles. Then the reaction of arylidenemalononitriles with pyrazolinones leads to pyranopyrazoles **5**.[3,4]

Later, a report[21] on four-component synthesis of 6-amino-4-aryl-3-methyl-4*H*-pyrazolo[3,4-*b*]pyrans in water has been published.

We employed cyclic ketones: *N*-substituted piperidin-4-ones **6a,b** and isatins **7a—c** in the four-component reaction to expand the synthetic potential of this reaction and to investigate the possibility of the synthesis of spiro-fused heterocyles. It was found that these ketones have

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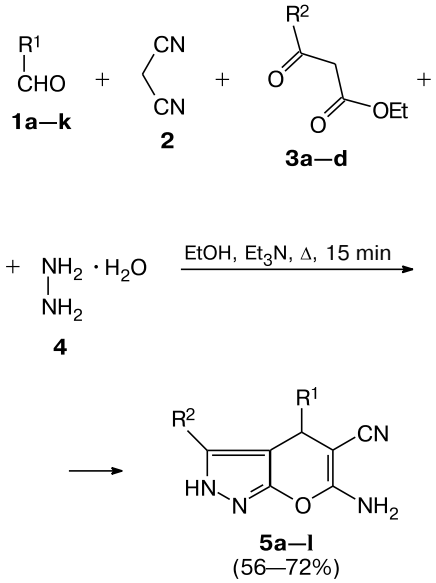
Scheme 1



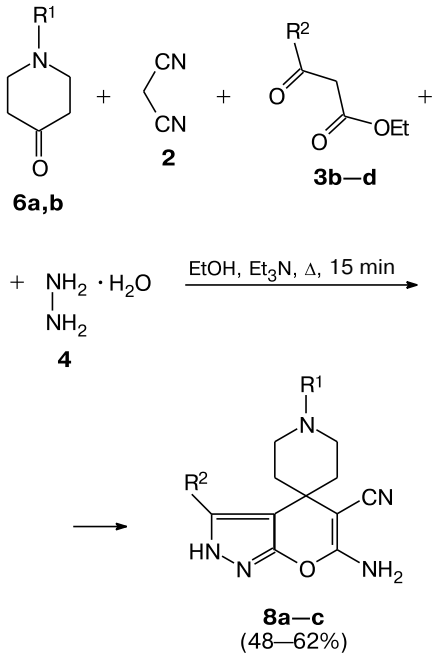
1: R^1 = Ph (**a**), 2,6-$F_2C_6H_3$ (**b**), 2,6-$Cl_2C_6H_3$ (**c**), 4-$(CF_3)C_6H_4$ (**d**), $(MeOOC)C_6H_4$ (**e**), 4-$Me_2NC_6H_4$ (**f**), 3-HOC_6H_4 (**g**), 2,5-$(MeO)_2C_6H_3$ (**h**), 3-(MeO)-4-$(PhCH_2O)C_6H_3$ (**i**), 3-C_4H_3O (**j**), 2-C_4H_3S (**k**)
3: R^2 = Ph (**a**), Me (**b**), Pr^n (**c**), CH_2OMe (**d**)

Compound	R^1	R^2
5a	Ph	Ph
5b	2,6-$F_2C_6H_3$	Me
5c	2,6-$Cl_2C_6H_3$	Me
5d	4-$(CF_3)C_6H_4$	Me
5e	4-$(MeOOC)C_6H_4$	Me
5f	4-$Me_2NC_6H_4$	Pr^n
5g	3-HOC_6H_4	CH_2OMe
5h	2,5-$(MeO)_2C_6H_3$	Me
5i	3-(MeO)-4-$(PhCH_2O)C_6H_3$	Me
5j	3-C_4H_3O	CH_2OMe
5k	3-C_4H_3O	Ph
5l	2-C_4H_3S	Me

different reactivities under conditions of the four-component reaction with malononitrile **2**, β-keto esters **3b—d**, and hydrazine hydrate **4**. The reaction faces no difficulties in the case of piperidin-4-ones **6a,b** and leads to the formation of spiro-fused pyrano[2,3-*c*]pyrazoles **8a—c** in 48—62% yields, the N—COMe and N—COOEt groups remaining intact (method *A*) (Scheme 2).

In the case of isatin **7a**, the reaction occurs with the formation of stable isatin monohydrazone **9** despite simultaneous addition of other reactants, *i.e.*, malononitrile **2**, ethyl acetoacetate **3b**, and hydrazine hydrate **4**, regardless of duration of heating (5—30 min). Product **9** was also formed in the reaction of preformed 2-(2-oxo-1,2-dihydro-3*H*-indole-3-ylidene)malononitrile **10** with ethyl acetoacetate **3b** and hydrazine hydrate **4**. However, having changed the order of mixing the reactants, we developed a new one-pot modification of the four-component reaction (method *B*). Initially, the reaction of the

Scheme 2



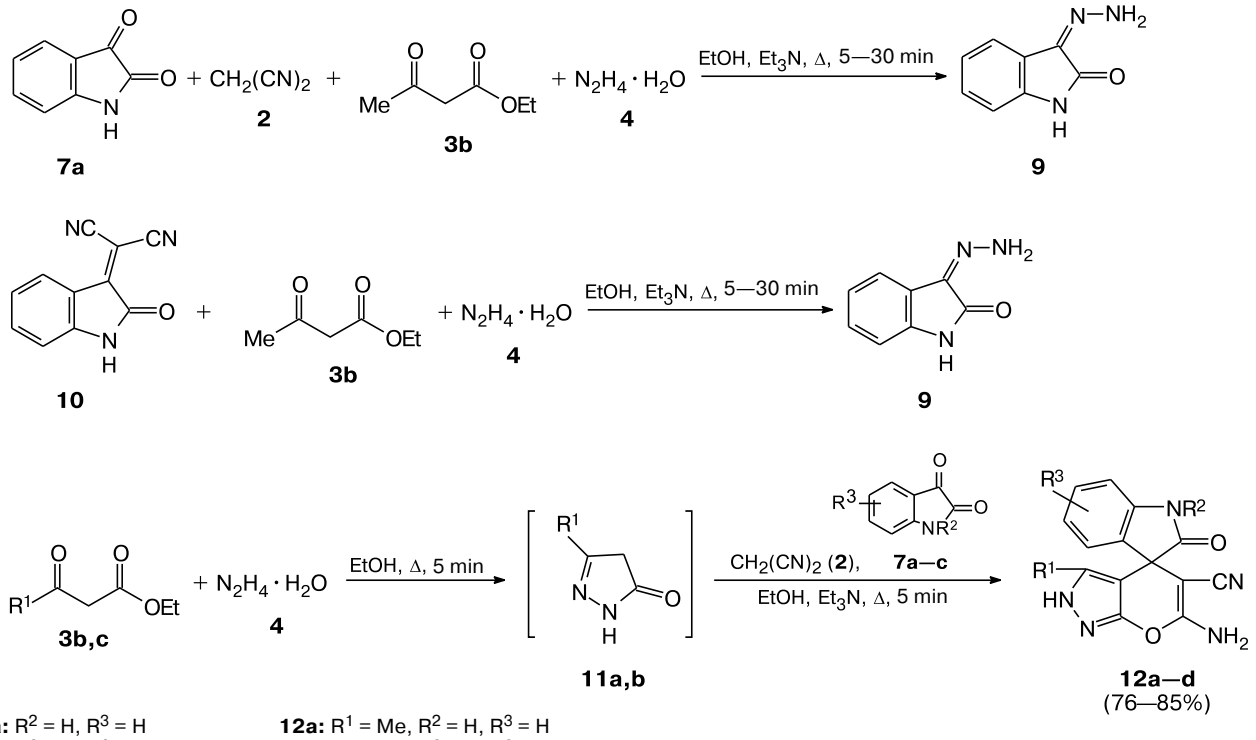
6: R^1 = COMe (**a**), COOEt (**b**)
3: R^2 = Me (**b**), Pr^n (**c**), CH_2OMe (**d**)
8: R^1 = COMe, R^2 = Pr^n (**a**); R^1 = COMe, R^2 = CH_2OMe (**b**); R^1 = COOEt, R^2 = Me (**c**)

corresponding β-keto ester **3b,c** with hydrazine hydrate was carried out in refluxing ethanol (5 min). Then, to pyrazolinones **11a,b** that formed, isatin **7a—c**, malononitrile **2**, and triethylamine were added, and reflux was continued for 5 min. Compounds **12a—d** were obtained under these conditions in 76—85% yields (Scheme 3).

Possibly, in this case isatins **7a—c** react with malononitrile **2** to form unsaturated nitriles of type **10**, which add pyrazolinone **11** with the closure of the pyran ring. It is important to note that in the case of **12a** the yield of the product was higher than in previous studies where this compound was obtained from unsaturated nitrile **10** and 5-methyl-2,4-dihydro-3*H*-pyrazole-3-one **11a** (54%)[13] or isatin **7a**, malononitrile **2**, and pyrazolinone **11a** (74%).[14]

The developed four-component method for synthesis of pyranopyrazoles consisted of reaction in ethanol in the presence of a base, triethylamine. These conditions impose one more limitation on the variation of the starting components. The replacement of hydrazine hydrate **4** by phenylhydrazine **13** resulted in benzaldehyde phenylhydrazone **14** (see Ref. 22) as a single crystalline reaction product in the four-component condensation with benzaldehyde **1a**, malononitrile **2**, and ethyl acetoacetate **3b** regardless of the reaction duration (Scheme 4). Thus, the four-component reaction gives an access only to *N*-unsubstituted pyrano[2,3-*c*]pyrazoles under the conditions found.

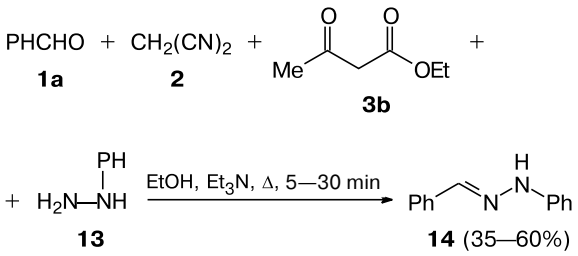
Scheme 3



7a: R^2 = H, R^3 = H
7b: R^2 = H, R^3 = 7-Me
7c: R^2 = Pr, R^3 = H
11: R^2 = Me (**a**), Pr^n (**b**)

12a: R^1 = Me, R^2 = H, R^3 = H
12b: R^1 = Me, R^2 = H, R^3 = 7-Me
12c: R^1 = Me, R^2 = Pr^n, R^3 = H
12d: R^1 = Pr^n, R^2 = H, R^3 = 7-Me

Scheme 4



The structures of all the obtained compounds **5**, **8**, and **10** were established based on data from elemental analysis, IR and ^{1}H NMR spectroscopy. A characteristic feature of the IR spectra is the presence of a band of stretching vibrations of the conjugated C≡N group in the region 2204—2180 cm^{-1} and bands ν(NH), ν(NH_2) at 3474—3168 cm^{-1}, which is in accord with the spectral data for the analogs that have previously been described.[1—12] All the compounds are characterized be the presence of signals of 6-NH_2 (δ 6.70—6.92, br.s, 2 H) and 2-NH (δ 12.04—12.87, br.s, 1 H) in the ^{1}H NMR spectra. A characterictic feature of the spectra of compounds **5a—l** is the presence of the signal for H(4) (δ 4.56—5.16, s, 1 H). ^{1}H NMR spectra of compounds **12a—d** are characterized by the presence of the NH proton signal of the oxindole fragment (δ 10.51—10.60, br.s, 1 H). The presence of the signals of alkyl (**5b—j,l**, **8a—c**, **12a—d**) and aryl (**5a—l, 12a—d**) substituents also corroborates the structure of the obtained compounds. Melting points, data from elemental analysis, IR and ^{1}H NMR spectroscopy for compounds **5**, **8**, and **12** are presented in Table 1.

Thus, in the present work it is shown that the convenient one-step four-component synthesis of pyrano-[2,3-*c*]pyrazoles can be used for the preparation of 4-aryl-substituted and spiro-fused heterocycles. When the synthesis is carried out with isatins, it can be easily transformed into a two-step one-pot procedure.

Experimental

The starting compounds were commercially available from Lancster. All the synthesized compounds were characterized by elemental analysis, IR and ^{1}H NMR spectroscopy. ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments (250 and 300 MHz, respectively) in DMSO-d_6, Me_4Si was used as the internal standard. IR spectra were obtained on a Fourier spectrometer Specord M-82 in KBr pellets (1 : 200 w/w). The control over the course of reactions and the purity of the synthesized compounds were carried out by TLC on Silufol UV-254 plates, light petroleum—acetone (5 : 3), visualization by iodine vapor. Melting points of the synthesized

Table 1. Yield, physical constants, and spectral characteristics of compounds **5, 8**, and **12**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	IR spectrum, ν/cm^{-1} (ν(NH), ν(C≡N), ν(C=O), δ(NH$_2$), ν(C=C))	^{1}H NMR, δ (*J*/Hz)
			C	H	N			
5a	65	275—276	72.70 72.60	4.33 4.49	17.69 17.82	$C_{19}H_{14}N_4O$	3484, 3208, 3108, 2204, 1636, 1588	4.98 (s, 1 H, H(4)); 6.88 (br.s, 2 H, NH$_2$); 7.19 (m, 10 H, 2 Ph); 12.87 (br.s, 1 H, NH)
5b	67	272—273	58.45 58.34	3.46 3.50	19.52 19.44	$C_{14}H_{10}F_2N_4O$	3398, 3360, 3280, 3176, 2184, 1652, 1596	1.85 (s, 3 H, Me); 5.03 (s, 1 H, H(4)); 6.81 (br.s, 2 H, NH$_2$); 7.04 (m, 2 H, H(3′), H(5′)); 7.35 (m, 1 H, H(4′)); 12.00 (br.s, 1 H, NH)
5c	70	249—250	52.44 52.36	3.08 3.14	17.36 17.44	$C_{14}H_{10}Cl_2N_4O$	3368, 3312, 3176, 2192, 1648, 1600	1.80 (s, 3 H, Me); 5.16 (s, 1 H, H(4)); 6.94 (br.s, 2 H, NH$_2$), 7.21 (t, 1 H, H(4′), *J* = 8.2); 7.35 (d, 2 H, H(3′), H(5′), *J* = 8.3); 12.10 (br.s, 1 H, NH)
5d	72	244—245	56.22 56.25	3.51 3.46	17.27 17.49	$C_{15}H_{11}F_3N_4O$	3480, 3232, 3120, 2192, 1 640, 1596	1.79 (s, 3 H, Me); 4.75 (s, 1 H, H(4)); 6.96 (br.s, 2 H, NH$_2$); 7.41 (d, 2 H, H(2′), H(6′), *J* = 7.7); 7.69 (d, 2 H, H(3′), H(5′), *J* = 7.7); 12.15 (br.s, 1 H, NH)
5e	68	240—242	61.75 61.93	4.37 4.55	18.21 18.05	$C_{16}H_{14}N_4O_3$	3376, 3312, 3192, 2184, 1724, 1648, 1600	1.79 (s, 3 H, Me); 3.85 (s, 3 H, COOC<u>H</u>$_3$); 4.72 (s, 1 H, H(4)); 6.92 (br.s, 2 H, NH$_2$); 7.34 (d, 2 H, H(2′), H(6′), *J* = 8.2); 7.34 (d, 2 H, H(3′), H(5′), *J* = 7.9); 12.12 (br.s, 1 H, NH)
5f	64	205—207	66.82 66.85	6.49 6.55	21.71 21.66	$C_{18}H_{21}N_5O$	3488, 3248, 3112, 2200, 1632, 1596	0.67 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$, *J* = 7.4); 1.14—1.35 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$); 2.01—2.23 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$); 4.45 (s, 1 H, H(4)); 6.65 (m, 4 H, H(3′), H(5′), NH$_2$); 6.95 (d, 2 H, H(2′), H(6′), *J* = 8.8); 11.99 (br.s, 1 H, NH)
5g	56	227—229	60.18 60.40	4.85 4.73	18.74 18.78	$C_{15}H_{14}N_4O_3$	3456, 3296, 3192, 2192, 1632, 1592	3.03 (s, 3 H, Me); 3.98 (AB system, 2 H, Me, *J* = 13.2); 4.53 (s, 1 H, H(4)); 6.55 (s, 1 H, H(2′)); 6.62 (d, 2 H, H(4′), H(6′), *J* = 7.4); 6.80 (br.s, 2 H, NH$_2$); 7.10 (t, H(5′), *J* = 7.7); 9.23 (s, 1 H, OH); 12.44 (br.s, 1 H, NH)
5h	61	243—244	61.57 61.53	5.15 5.16	17.96 17.94	$C_{16}H_{16}N_4O_3$	3320, 3168, 2200, 1660, 1616, 1600	1.82 (s, 3 H, Me); 3.65 (s, 3 H, OMe); 3.73 (s, 3 H, OMe); 4.92 (s, 1 H, H(4)); 6.53 (d, 1 H, H(6′), *J* = 2.8); 6.70 (br.s, 2 H, NH$_2$); 6.77 (dd, 1 H, H(4′), *J* = 3.0, *J* = 8.9); 6.93 (d, 1 H, H(3′), *J* = 8.7); 11.95 (br.s, 1 H, NH)
5i	56	221—223	67.76 68.03	5.23 5.19	14.65 14.42	$C_{22}H_{20}N_4O_3$	3464, 3248, 3112, 2184, 1644, 1596	1.84 (s, 3 H, Me); 3.73 (s, 3 H, OMe); 4.56 (s, 1 H, H(4)); 5.04 (s, 2 H, PhC<u>H</u>$_2$O); 6.68 (d, 1 H, H(5′), *J* = 7.9); 6.72 (br.s, 2 H, NH$_2$); 6.80 (s, 1 H, H(2′)); 6.99 (d, 1 H, H(6′), *J* = 7.9); 7.32—7.46 (m, 5 H, Ph); 12.01 (br.s, 1 H, NH)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1} (ν(NH), ν(C≡N), ν(C=O), δ(NH_2), ν(C=C))	^{1}H NMR, δ (*J*/Hz)
5j	62	233—235	57.54 57.35	4.24 4.44	20.62 20.58	$C_{13}H_{12}N_4O_3$	3408, 3296, 3192, 2200, 1632, 1600	3.11 (s, 3 H, Me); 4.10 (AB system, 2 H, Me, *J* = 12.9); 4.64 (s, 1 H, H(4)); 6.23 (s, 1 H, H(4′)); 6.83 (br.s, 2 H, NH_2); 7.56 (s, 2 H, H(2′), H(5′)); 12.48 (br.s, 1 H, NH)
5k	65	228—230	67.19 67.10	3.82 3.97	18.62 18.41	$C_{17}H_{12}N_4O_2$	3488, 3128, 2200, 1636, 1604	4.97 (s, 1 H, H(4)); 6.10 (s, 1 H, H(4′) C_4H_3O); 6.69 (br.s, 2 H, NH_2); 7.16—7.24 (m, 1 H, ArH); 7.32—7.40 (m, 4 H, ArH); 7.53—7.55 (m, 2 H, ArH); 12.70 (br.s, 1 H, NH)
5l	70	258—260	55.54 55.80	3.91 3.90	21.84 21.69	$C_{12}H_{10}N_4OS$	3369, 3320, 3168, 2192, 1648, 1592	1.92 (s, 3 H, Me); 4.99 (s, 1 H, H(4)); 6.95 (m, 3 H, ArH + NH_2); 7.01 (m, 1 H, ArH); 7.37 (d, 1 H, ArH, *J* = 5.3); 12.18 (br.s, 1 H, NH)
8a	59	199—201 (199—200)[11]	60.78 60.94	6.42 6.71	22.34 22.21	$C_{16}H_{21}N_5O_2$	3392, 3312, 3192, 2192, 1668, 1638	0.88 (t, 3 H, C$\underline{H}_3$CH$_2$CH$_2$, *J* = 7.0); 1.80—1.82 (m, 4 H); 1.87 (m, 2 H); 1.97 (m, 2 H) (MeC$\underline{H}_2$C$\underline{H}_2$ + + (C$\underline{H}_2$C$\underline{H}_2$)N); 2.02 (s, 3 H, MeCO); 3.39 (m, 1 H); 3.73 (m, 2 H); 4.21 (m, 1 H, (C$\underline{H}_2$C$\underline{H}_2$)N); 6.81 (br.s, 2 H, NH_2); 12.15 (br.s, 1 H, NH)
8b	62	175—176 (176—177)[11]	56.53 56.77	5.91 6.03	21.79 22.07	$C_{15}H_{19}N_5O_3$	3392, 3317, 3200, 2196, 1672, 1642	1.80—2.04 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$); 2.26 (s, 3 H, MeCO); 3.18 (s, 3 H, MeOCH_2); 3.42 (m, 1 H); 3.73 (m, 1 H); 3.86 (m, 1 H); 4.22 (m, 1 H, (C$\underline{H}_2$C$\underline{H}_2$)$_2$N); 4.36 (s, 2 H, MeOC$\underline{H}_2$); 6.87 (br.s, 2 H, NH_2); 12.56 (br.s, 1 H, NH)
8c	48	187—188	56.77 56.91	6.12 6.03	21.98 22.07	$C_{15}H_{19}N_5O_3$	3400, 3308, 3184, 2180, 1676, 1640	1.21 (t, 3 H, C$\underline{H}_3$CH$_2$ *J* = 7.8); 1.80, 1.95, 3.58, 3.84 (all m, 2 H each, C(C$\underline{H}_2$C$\underline{H}_2$)$_2$N); 2.25 (s, 3 H, Me); 4.10 (q, 2 H, MeC$\underline{H}_2$, *J* = 8.0); 6.70 (br.s, 2 H, NH_2); 12.10 (br.s, 1 H, NH)
12a	85	> 300 (285—286 °C, EtOH)[13]	61.62 61.43	3.59 3.78	23.81 23.88	$C_{15}H_{11}N_5O_2$	3408, 3316, 3136, 2932, 2196, 1708, 1640, 1592	1.55 (s, 3 H, Me); 6.92 (d, 1 H, H(7), *J* = 8.1); 7.02 (m, 2 H, H(4), H(5)); 7.11 (br.s, 2 H, NH_2); 7.25 (td, 1 H, H(6), *J* = 7.3, *J* = 1.9); 10.51 (br.s, 1 H, N(1′)H); 12.21 (br.s, 1 H, N(2′)H)
12b	79	>300	62.47 62.53	4.08 4.26	22.95 22.79	$C_{16}H_{13}N_5O_2$	3408, 3316, 3128, 2200, 1712, 1644, 1604, 1592	1.56 (s, 3 H, C(3′)Me); 2.27 (s, 3 H, C(7)Me); 6.88 (m, 2 H, H(5), H(6)); 7.06 (d, 1 H, H(4), *J* = 7.3); 7.13 (br.s, 2 H, NH_2); 10.58 (br.s, 1 H, N(1)H); 12.22 (br.s, 1 H, N(2′)H)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1} (ν(NH), ν(C≡N), ν(C=O), δ(NH$_2$), ν(C=C))	^{1}H NMR, δ (*J*/Hz)
12c	81	284—286	64.65 64.47	5.03 5.11	20.76 20.88	$C_{18}H_{17}N_5O_2$	3308, 3176, 2200, 1700, 1640, 1596	0.93 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$N, *J* = 7.3); 1.48 (s, 3 H, Me); 1.66 (m, 2 H, MeC<u>H</u>$_2$CH$_2$N); 3.69 (t, 2 H, MeCH$_2$C<u>H</u>$_2$N, *J* = 7.4); 7.08—7.14 (m, 6 H, H(4)—H(7), NH$_2$); 12.23 (br.s, 1 H, NH)
12d	76	>300	64.53 64.47	5.07 5.11	20.69 20.88	$C_{18}H_{17}N_5O_2$	3384, 3324, 3172, 2192, 1712, 1648, 1596	0.55 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$, *J* = 7.4); 1.04 (m, 2 H, MeC<u>H</u>$_2$CH$_2$); 1.85 (m, 2 H, MeCH$_2$C<u>H</u>$_2$); 2.27 (s, 3 H, C(7′)Me); 6.88 (m, 2 H, H(5), H(6)); 7.08 (m, 3 H, H(4) + NH$_2$); 10.57 (br.s, 1 H, N(1)H); 12.20 (br.s, 1 H, N(2′)H)

compounds were determined on a Boetius heating stage and were uncorrected. Elemental analysis was performed with a Perkin—Elmer 2400 microanalyzer.

6-Amino-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles 5a—l (general procedure). Malononitrile **2** (5 mmol), β-keto ester **3a—d** (5.5 mmol), and hydrazine hydrate **4** (5.5 mmol) were added to a solution of aldehyde **1a—k** (5 mmol) in ethanol (20 mL), then triethylamine (1 mmol) was added. The reaction mixture was refluxed for 15 min, cooled to 4 °C and kept at 4 °C for 16 h. The precipitate that formed was filtered off, washed with ethanol (2S5 mL), light petroleum (5 mL), and recrystallized from ethanol. The products that obtained were dried in a drying oven at 60—70 °C.

3′-Alkyl-6′-aminospiro[piperidin-4,4′-(2′*H*,4′*H*)-pyrano-[2,3-*c*]pyrazole]-5′-carbonitriles (8a—c) (general procedure). Malononitrile **2** (5 mmol), β-keto ester **3b—d** (5.5 mmol), and hydrazine hydrate **4** (5.5 mmol) were added to a solution of piperidin-4-one **6a,b** (5 mmol) in ethanol (20 mL), then triethylamine (1 mmol) was added. The reaction mixture was refluxed for 15 min, cooled to 4 °C and kept at 4 °C for 16 h. The precipitate that formed was filtered off, washed with ethanol (2×5 mL), light petroleum (5 mL), and recrystallized from ethanol. The products that obtained were dried in a drying oven at 60—70 °C.

3′-Alkyl-6′-amino-5′-cyano-1,2-dihydrospiro[(3*H*)-indole-3,4′-(4′*H*)-pyrano[2,3-*c*]pyrazole]-2-ones 12a—d (general procedure). A solution of β-keto ester **3b** or **3c** and hydrazine hydrate **4** (5.5 mmol each) in ethanol (20 mL) was refluxed for 5 min. Isatin **7a—c** and malononitrile **2** were added, and the reaction mixture was refluxed for additional 5 min. The reaction mixture was cooled to 4 °C and kept at 4 °C for 16 h. The precipitate that formed was filtered off, washed with ethanol (2×5 mL), light petroleum (5 mL), and recrystallized from ethanol. The products that obtained were dried in a drying oven at 60—70 °C.

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