New Convenient Four-Component Synthesis of 6-Amino-2,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitriles and One-Pot Synthesis of 6′-Aminospiro[(3*H*)-indol-3,4′-pyrano[2,3-*c*]pyrazol]-(1*H*)-2-on-5′-carbonitriles

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This report describes a new four-component synthesis of substituted and spiro-conjugated 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazol-5-carbonitriles directly from aromatic aldehydes or heterocyclic ketones, malononitrile, β-ketoesters, and hydrazine hydrate. The method provides a convenient one-pot route toward divers 2,4-dihydropyrano[2,3-*c*]pyrazoles, whereas a modified one-step sequential protocol gives access to spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-ones.

Substituted pyranopyrazoles have been described in literature as biologically important compounds. As such, substituted pyrano[2,3-*c*]pyrazol-6-ones have been shown as promising analgesic (mice, $ED_{50} \approx 6-200$ mg/kg)[1a−c] and antiplatelet molecules (washed rabbit platelets),[1d−f] which effect K^+-induced calcium-dependent aortal contaction.[1f] Several pyrano[2,3-*d*]pyrazol-4-ones have demonstrated an affinity toward A_1 and A_{2a} adenosine receptors.[1g,h] Pyrano[2,3-*c*]pyrazoles have been shown as compounds with potential anticancer,[1j] antibacterial,[1e,i] antifungal,[1e] anti-inflammatory,[1k] and molluscicidal activity.[1l,m] They have also been identified as promising human Chk1 kinase inhibitors in computer-based screening and kinase-ihibition assays.[1n] Whereas, spiro[(3′H)-indol-3′,4-(4H)-pyrano[2,3-*c*]pyrazoles] have attracted attention as potential antimicrobal[2a] and herbicidal[2b] agents.

Synthetic methods for 6-aminopyrano[2,3-*c*]pyrazol-5-carbonitriles were extensively studied in the past because of their promising biological potential. The first approach toward these compounds was based on the reaction of tetracyanoethylene with 3-methyl-1*H*-pyrazolin-5-one, which gives 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazol-4,4,5-tricarbonitriles in good yields.[3] Subsequently, 4-aryl[4] and 4-alkyl-substituted pyranopyrazoles,[5] and pyranopyrazoles with spiro-annulated piperidine[6] and 3-oxindole[2b,7] were reported. Some of the prepared pyranopyrazoles, such as 6-amino-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazol-5-carbonitrile, were consequently used as starting materials in the synthesis of complex annulated heterocycles.[8] The most common and convenient approach toward diverse pyranopyrazoles is a three-component base-[4a,b,d,e,5,7] or electro-catalyzed[6] reaction of aldehydes or cyclic ketones, malonodinitrile, and corresponding pyrazolin-5-ones. This methodology gives pyranopyrazoles in high yields and can be extended to prepare combinatorial libraries of 6-amino-2,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitriles.[5c] Another approach is based on a two-step procedure, which includes isolation of intermediate arylidenemalononitriles[4c,d,f] or 4-arylidenepyrazoline-5-ones.[4e,f] Notably, synthesis of pyrano[2,3-*c*]pyrazoles depend neither on the reagent addition order nor on the order of the reaction steps in the two-step protocol, and, in the simplest variation, all starting materials can be mixed and reacted together. One of the drawbacks of the previously described methods for pyranopyrazoles was the necessity to synthesize and isolate pyrazolin-5-ones, which are normally commercially unavailable and must be prepared in advance from the corresponding β-ketoesters and hydrazine hydrate.[9] Inspired by the remarkable selectivity of such four- and three-component condensations as Ugi,[10a,b] Hantzsch,[10c,d] Biginelli,[10e] and Gewald[10f,g] reactions, we decided to investigate the possibility of pyrano[2,3-*c*]pyrazole synthesis via four-component reaction

Table 1. Synthesis of 6-Amino-4-aryl-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazol-5-carbonitriles **5** by a Four-Component reaction

entry	yield (%)	entry	yield (%)
5{*1*,*1*}*	65	**5**{*16*,*3*}	59
5{*2*,*1*}*	72	**5**{*17*,*1*}	52
5{*3*,*1*}*	68	**5**{*18*,*1*}	50
5{*4*,*1*}	64	**5**{*19*,*1*}	47
5{*5*,*5*}	57	**5**{*20*,*5*}	54
5{*6*,*5*}	76	**5**{*21*,*3*}	67
5{*7*,*1*}	74	**5**{*22*,*3*}	61
5{*8*,*1*}	79	**5**{*23*,*3*}	72
5{*9*,*3*}	53	**5**{*24*,*3*}	75
5{*10*,*6*}	61	**5**{*24*,*5*}	63
5{*11*,*2*}	66	**5**{*25*,*2*}	55
5{*12*,*1*}	60	**5**{*25*,*3*}	53
5{*13*,*1*}	58	**5**{*26*,*1*}	49
5{*14*,*3*}	54	**5**{*27*,*3*}	54
5{*15*,*5*}	49		

* Reported in literature.

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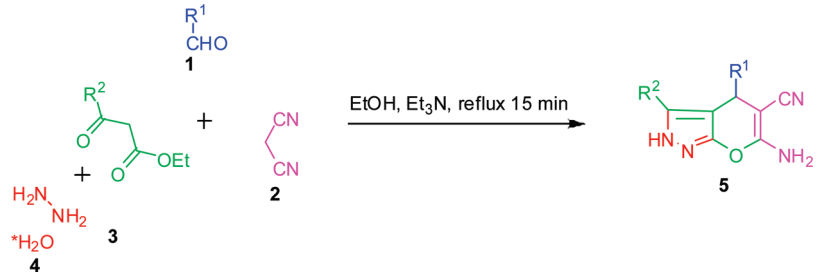
Scheme 1. Four-Component Pyrano[2,3-*c*]pyrazole Synthesis with Aromatic Aldehydes **1**{*1*−*27*}



directly from aromatic aldehydes, malononitrile, β-ketoesters and hydrazine hydrate.

In our preliminary studies, we demonstrated that a 4-component reaction of aromatic aldehydes **1**, malononitrile **2**, β-ketoesters **3,** and hydrazine hydrate **4** successfully yields 6-aminopyrano[2,3-*c*]pyrazol-5-carbonitriles without the need of prior pyrazolin-5-ones isolation.[11] Subsequently, this study was used to develop a four-component synthesis of diverse pyranopyrazoles. The multicomponent synthesis of pyranopyrazoles was carried out by simultaneously refluxing all four starting materials in ethanol for 15 min in the presence of Et_3N (Method A, Scheme 1). We demonstrated that this

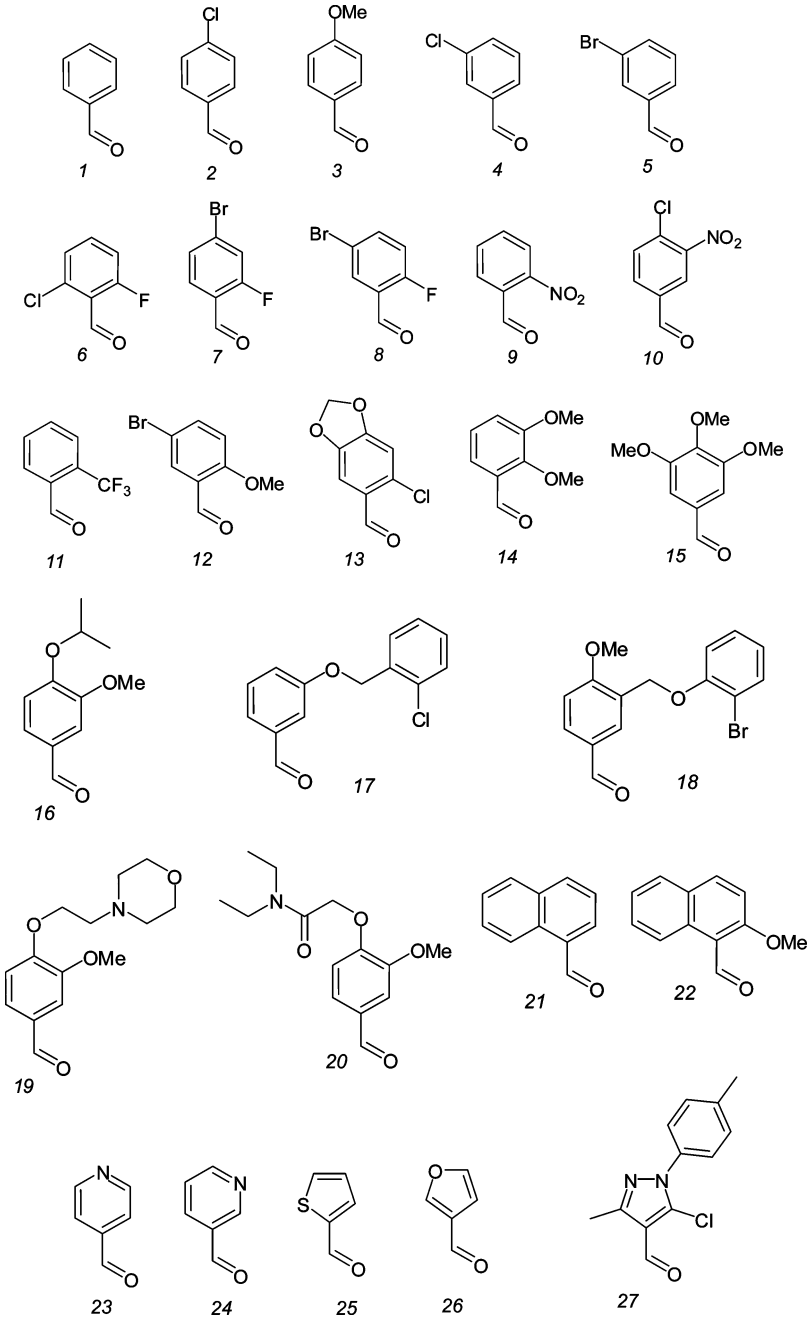


Figure 1. Chemical structures of aldehydes **1**{*1*−*27*}.

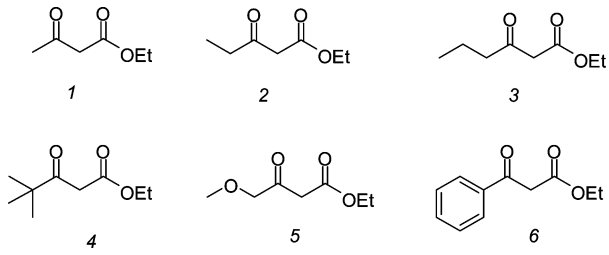


Figure 2. Chemical structures of β-ketoesters **3**{*1*−*5*}.

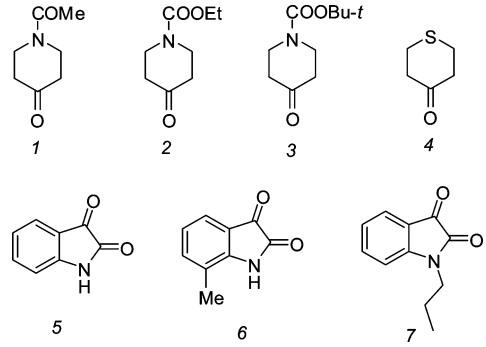


Figure 3. Structures of heterocyclic ketones **8**.

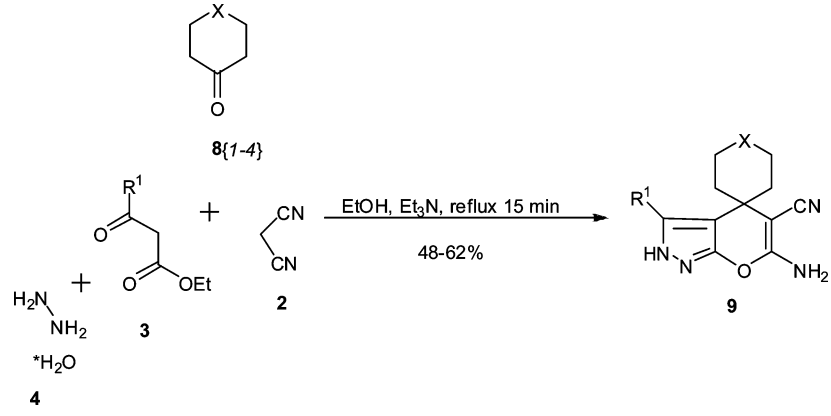
protocol accepts a wide variety of aromatic aldehydes **1**{*1*−*27*} and β-ketoesters **3**{*1*−*6*}, and produces pyrano[2,3-*c*]pyrazoles **5** in good yields (Scheme 1, Table 1). More specifically, we showed that aromatic aldehydes with electron-withdrawing **1**{*2*,*4*−*11*}, electron-donating **1**{*3*,*14*−*20*}, withdrawing and donating **1**{*12*,*13*} groups, as well as napthaldehydes **1**{*21*,*22*} and heteroaromatic aldehydes **1**{*23*−*27*} can be successfully reacted with β-ketoesters **3**{*1*−*3*,*5*,*6*}, malonodinitrile **2**, and hydrazine hydrate **4** to yield final pyrano[2,3-*c*]pyrazoles **5** with high regio-selectivity. At the same time, four-component reactions with pyvaloylacetic ester **3** {*4*} were unsuccessful, most likely, because of the steric constraints.

Table 2. Synthesis of Spiro-annulated Pyranopyrazoles **9** and **12**

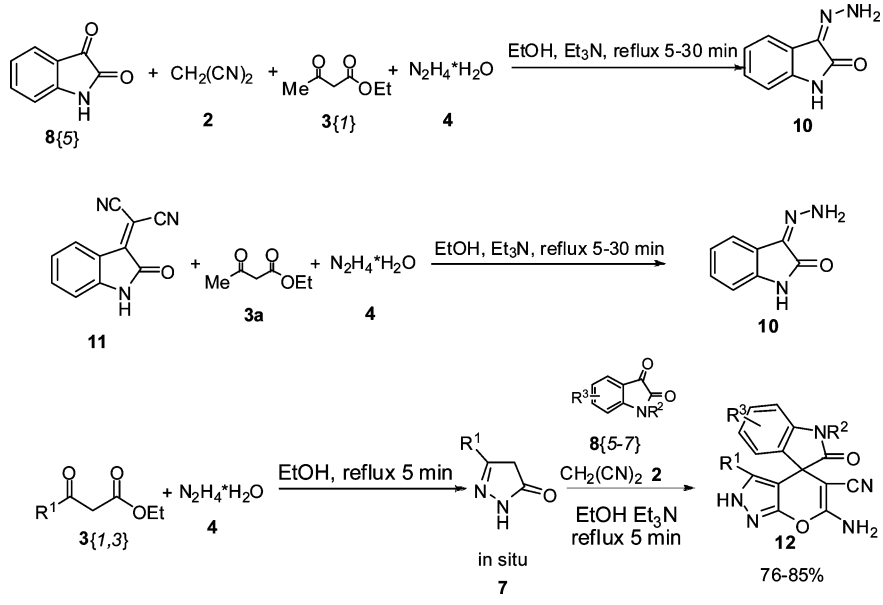
entry	yield (%) (method)
9{*3*,*1*}	59 (A)
9{*4*,*1*}	62 (A)
9{*1*,*2*}	48 (A)
9{*1*,*3*}	57 (A)
9{*1*,*4*}	46 (A)
12{*1*,*5*}	85 (B)
12{*1*,*6*}	79 (B)
12{*1*,*7*}	81 (B)
12{*3*,*6*}	76 (B)

Previously in literature, a four-component synthesis of 6-amino-4-aryl-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazol-5-car-

Scheme 2. Four-Component Pyrano[2,3-*c*]pyrazole Synthesis with Saturated Heterocyclic Ketones **8**{*1*−*4*}



Scheme 3. Sequential Pyrano[2,3-*c*]pyrazole Synthesis with Isatins **8**{*5*−*7*}



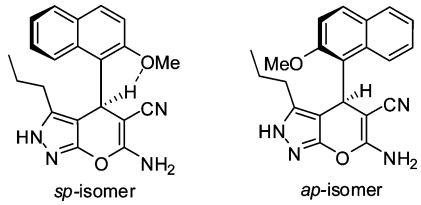


Figure 4. Atropisomers of **5**{*22*,*3*}.

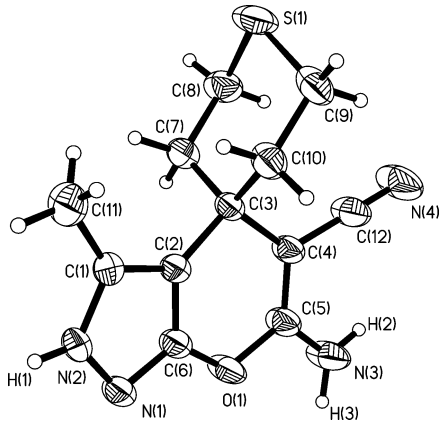


Figure 5. Molecular structure of **9**{*1*,*4*}.

bonitriles was carried out in water.[12] In this protocol components **1, 2** and catalytic amount of piperidine were added to a vigorously stirred aqueous solution of **3**{*1*} and **4** during a period of 10−15 min. Subsequently, the resulting mixture was washed with hexane/EtOAc 4:1 to isolate the products. Although promoted as ecologically friendly synthesis, this protocol failed to account for copious amounts of organic solvents, which were required to work up the reaction. Moreover, our attempts to reproduce this procedure on pyrano[2,3-*c*]pyrazoles **5**{*2*} and **5**{*3*} yielded complex mixtures of intermediates and products, separable only by chromatography (see Supporting Information for H NMR comparison).

To broaden the scope of the reaction and to prepare spiro-conjugated pyrano[2,3-*c*]pyrazoles we used heterocyclic ketones such as N-substituted piperidin-4-ones **8**{*1*−*3*}, tetrahydrothiopyran-4-one **8**{*4*}, and isatins **8**{*5*−*7*} as the starting materials (Figure 3). Saturated cyclic ketones **8**{*1*−*4*} were reacted with malonodinitrile, hydrazine, and ketoesters **3** to yield spiro-annulated pyrano[2,3-*c*]pyrazoles **9** in 45−62% yields (Table 2). The reaction was complete after refluxing for 15 min, and it did not modify *N*-COMe and *N*-COOR groups (Scheme 2).

The four-component reaction with isatine **8**{*5*} produced stable isatine monohydrazone **10** independent of the reaction time (5−30 min). Similarly, a three-component reaction of 3-(dicyanomethylene)-2-oxindole **11** with ketoesters **3** and hydrazine also failed to produce desired pyrano[2,3-*c*]pyrazole, and instead yielded the same monohydrazone **10** (Scheme 3). However, by changing the reactant addition sequence we developed a one-pot sequential protocol that gives pyrano[2,3-*c*]pyrazole spiro-conjugated with isatins (method B). First, the reaction mixture of ketoester **3** and hydrazine hydrate is heated in ethanol for 5 min. Then, isatine **8**{*5*}, malononitrile **2**, and Et_3N are added simultaneously to the reaction mixture, and the heating is continued for

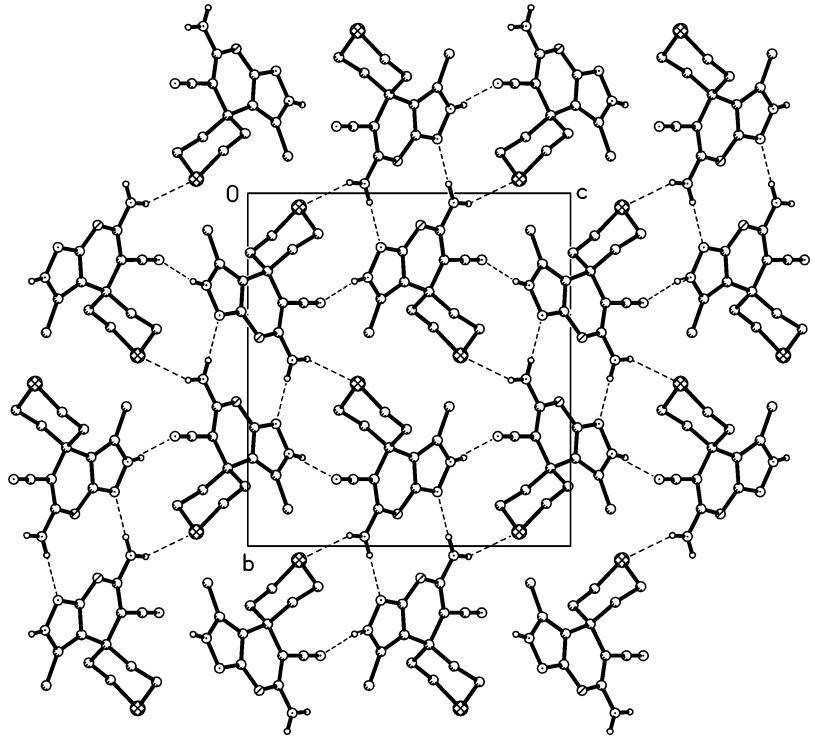
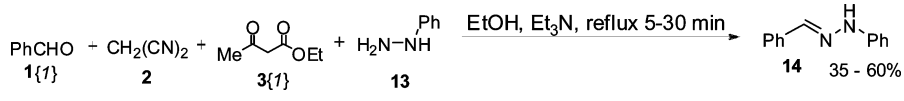


Figure 6. Crystal structure of **9**{*1*,*4*}.

Scheme 4. Formation of 1-Benzylidene-2-Phenylhydrazine **14** in Four-Component Reaction with Phenylhydrazine **13**



additional 5 min. This procedure accepts a variety of isatins **8**{*5*−*7*} and ketoesters **3** and gives desired products **12** in high yield (Scheme 3, Table 2).

The yield of compound **12**{*1*,*5*} (85%) prepared by our method was significantly higher, than in previously reported protocols (54[7a] and 74,[7c] respectively). Moreover, the previously reported melting point of **12**{*1*,*5*}[7c] is significantly lower (175−177 °C) than our result (>300 °C dec.), which suggests that the developed method affords pyrano[2,3-*c*]pyrazoles **12** with higher purity and better yields.

Although the developed method can accept a wide variety of aldehydes **1** and ketoesters **3** as starting materials, we were unable to extend it to include substituted hydrazines. As such, a four-component reaction of phenylhydrazine **13** with benzaldehyde **1**{*1*}, malononitrile **2**, and ethyl acetoacetate **3**{*1*} produced 1-benzylidene-2-phenylhydrazine **14** as the only crystalline product (Scheme 4). Nonetheless, we continue to explore abilities of the developed method to prepare N-substituted pyrano[2,3-*c*]pyrazoles and will report our results in the future.

The structures and purity of compounds **5**, **9**, and **12** were confirmed by the elemental analysis, IR-spectroscopy, and ^{1}H NMR. The IR-spectra of all pyrano[2,3-*c*]pyrazoles contain characteristic absorption bands of a conjugated cyano-group at 2204−2180 cm^{-1} and ν(NH), ν(NH$_2$) absorption bands at 3488−3120 cm^{-1}.[3,4b−f,5−8,12−14] ^{1}H NMR spectra contain signals of 6-NH$_2$ (6.50−7.13 ppm, br s, 2H) and 2-NH (11.95−12.87 ppm, br s, 1H) groups, as well as signals of aliphatic (0.67−5.04 ppm) and aromatic protons (6.23−7.69 ppm). ^{1}H NMR spectra of compounds **5** show H4 (4.50−5.80 ppm, s, 1H) signals, whereas spectra of **12** contain characteristic NH peaks of oxindole moiety (10.51−10.60 ppm, br. s, 1H). ^{1}H NMR spectra of pyranopyrazoles with 4-(1-napthyl) substituents (**5**{*21*,*3*} and **5**{*22*,*3*}) demonstrate an atropisomerism phenomenon because of the rotation around C(4)−C$_{10}$H$_7$ bond. Earlier in literature, the intramolecular contact between C(4)H and 8-naphthyl protons in 4-(1-napthyl) substituted aminopyrans was suggested as a reason for a hindered internal rotation (X-ray analysis data).[13] Similarly, a rotation of a bulky naphthalene ring in pyrano[2,3-*c*]pyrazoles **5** can be sterically constrained because of the intramolecular contacts with n-propyl or cyano groups. The 1H NMR spectrum of **5**{*21*,*3*} with unsubstituted napthyl group at 299 K shows H4 proton and ortho- and peri-protons as broad singlets, which suggests that the coalescence temperature is close to room temperature and that at these conditions the rotation barrier is not high enough for atropisomers to be separated. In contrast, the ^{1}H NMR of pyran **5**{*22,3*} with 2-methoxynaphtyl-1 group clearly contains two atropisomers (ratio 2:1), which is indicated by a doubling effect of H4, OCH$_3$, aromatic protons and even 2-NH, 6-NH$_2$ and propyl protons (See Supporting info). Significant downfield shifts of H4 and OCH$_3$ signals can be explained by the intramolecular hydrogen bond in sp-isomer (Figure 4).[14]

The X-ray analysis of **9**{*1*,*4*} confirmed spiro-conjugated structure (Figure 5). In molecule **9**{*4*,*1*}, the mean deviation of atoms O(1), N(1,2), and C(1, 2, 4, 5) from mean quadratic plane does not exceed 0.03 Å; however atom C(3) comes out of it by 0.19 Å. Six-membered cycle C(3)C(7)C(8)S(1)-C(9)C(10) adopts chair conformation (torsion angles around bonds C(10)−C(9), C(9)−S(1), S(1)−C(8), C(8)−C(7), C(7)−C(3), and C(3)−C(10) are 56.1, −54.0, 56.1, −61.8, 54.5, and −50.8°, respectively).

The crystal structure of **9**{*4*,*1*} is lamellar (Figure 6). All "active" hydrogen atoms participate in intermolecular hydrogen bond formation, which unite molecules into parallel planes (1 0 2). Basic crystallographic parameters, results of structure refinement, atom coordinates, and thermal parameters are given in the Supporting Information.

In conclusion, we have developed a new convenient four-component method of synthesis of 6-aminospiro[(3′*H*)-indol-3,4′-pyrano[2,3-*c*]pyrazol]-(1′*H*)-2′-on-5-carbonitriles. The protocol accepts a variety of aromatic aldehydes, piperidin-4-ones, and tetrahydrothiopyran-4-one as starting materials and gives pyrano[2,3-*c*]pyrazoles in good to high yield. The method provides a convenient one-pot route toward diverse 2,4-dihydropyrano[2,3-*c*]pyrazoles, whereas a modified one-step sequential protocol gives access to spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-ones.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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