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# Cross-condensation of derivatives of cyanoacetic acid and carbonyl compounds. Part 1: Single-stage synthesis of 1′-substituted 6-amino-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitriles

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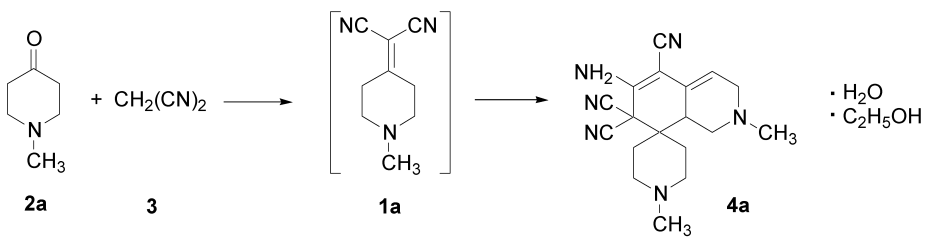
**Abstract**—To develop a method of synthesis of the potentially physiologically active compounds, 1′-substituted 6-amino-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles, we studied the three-component condensation of substituted piperidin-4-ones, malononitrile and pyrazolin-5-ones. It was found that the electrochemical method of synthesis is more regioselective, the products of the reaction are analytically pure and do not require further recrystallization.


## 1. Introduction

Substituted 6-amino-4*H*-pyrano[2,3-*c*]pyrazoles have been synthesized in a search for new physiologically active compounds, drugs, pesticides, and other compounds of practical significance.[1–7] The first representative of this class of compounds was prepared by the reaction of 5-methyl-2-phenyl-1,2-dihydropyrazol-3-one and tetracyanoethylene.[2] Later 6-amino-4*H*-pyrano[2,3-*c*]pyrazoles were synthesized by the reaction of arylidenemalononitriles with 3-methylpyrazolin-5-one or condensation of 4-arylidenepyrazolin-5-ones with malononitrile.[3–7] Sharanin and co-authors developed the simplest method for synthesis of these compounds: three-component condensation of aromatic aldehydes, malononitrile, and substituted pyrazolin-5-ones.[4–7]

## 2. Results and discussion

In order to expand the method of synthesis of the potentially physiologically active 1′-substituted 6-amino-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles, we decided to replace aromatic aldehydes in the three-component condensation by a series of N-substituted piperidin-4-ones. Preliminary results have been published.[8] At first we attempted to obtain unsaturated nitrile (**1a**, Scheme 1) in ethanol by the condensation of 1-methylpiperidin-4-one (**2a**) and malononitrile (**3**). The resulting compound is unstable and dimerized in the presence of triethylamine at room temperature to form spiro-piperidinoisoquinoline (**4a**) within 2–3 min after mixing the reactants (chromatographic monitoring). Probably the basic 1-methylpiperidin-4-one reactant, **2a**, also favors cyclohexylidenemalononitrile




**Scheme 1.**

*Keywords*: pyran; pyrazole; pyranopyrazole; piperidinone; Michael adduct; spiro compounds.
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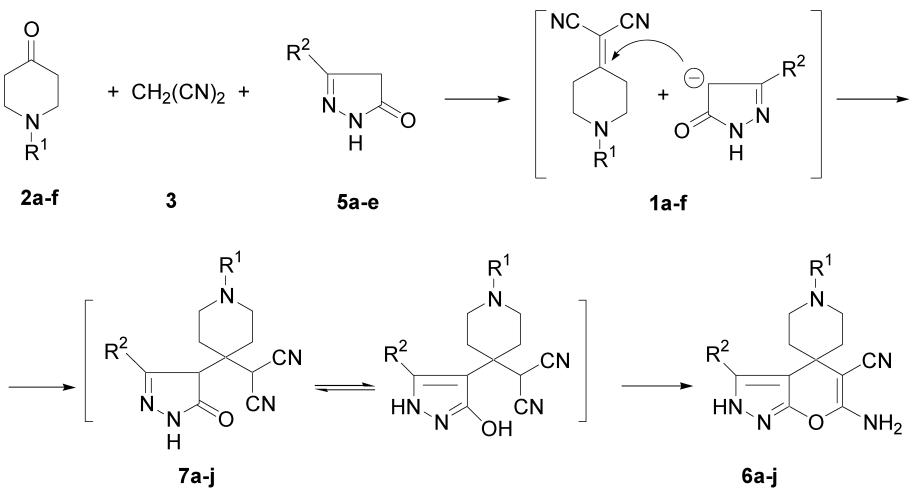
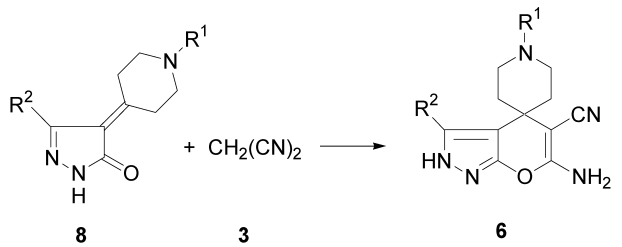



**Scheme 2.** *Reagents and conditions*: **2a**, **6c**,**e**,**f** $R^1$=Me; **2b**, **6a**,**b** $R^1$=H; **2c**, **6d** $R^1$=Et; **2d**, **6g** $R^1$=$CH_2CH_2Ph$; **2e**, **6h**,**i** $R^1$=C(O)Me; **2f**, **6j** $R^1$=COOEt; **5a**, **6a**,**c**,**d**,**g** $R^2$=Me; **5b**, **6b** $R^2$=Et; **5c**, **6e**,**h**,**j** $R^2$=$CH_2OMe$; **5d**, **6f** $R^2$=Ph; **5e**, **6i** $R^2$=*n*-Pr.

dimerization to form the substituted spiro-cyclohexane-decahydronaphthalene.[9]

Then we studied the three-component condensation of substituted piperidin-4-ones, **2**, malononitrile, **3**, and pyrazolin-5-ones (**5**, Scheme 2). Substituted spiro-4,4′-piperidinopyrano[2,3-*c*]pyrazoles (**6**) were obtained as the products of the reaction after a short refluxing in ethanol in the presence of triethylamine (method A). Taking into account that compound **4** is also formed without a catalyst, we studied the regioselectivity of the condensation of piperidin-4-ones, **2**, pyrazolin-5-ones, **5**, and malononitrile, **3**, without triethylamine. In this case, the three-component condensation of the above compounds in ethanol at room temperature (method B) affords spiro-4,4′-piperidino-pyrano[2,3-*c*]pyrazoles, **6**, in a higher yield (by 8–10%) compared to method A. This regioselectivity can probably be explained by Scheme 2, where the nucleophilic addition of the pyrazoline-5-one, **5**, to the initially formed unsaturated nitrile, **1**, predominates over the dimerization of **1**.




**Scheme 3**. *Reagents and conditions*: **6a**,**b** $R^1$=H; **6c**,**e**,**f** $R^1$=Me; **6d** $R^1$=Et; **6g** $R^1$=$CH_2CH_2Ph$; **6h**,**i** $R^1$=C(O)Me; **6j** $R^1$=COOEt; **6a**,**c**,**d**,**g** $R^2$=Me; **6b** $R^2$=Et; **6e**,**h**,**j** $R^2$=$CH_2OMe$; **6f** $R^2$=Ph; **6i** $R^2$=*n*-Pr.

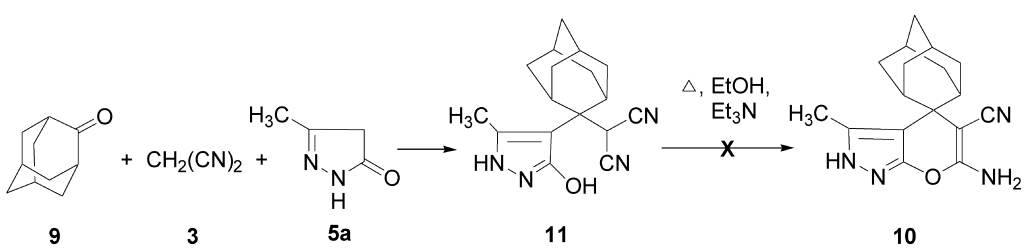
The subsequent intramolecular cyclization of the Michael adducts (**7**) results in the compounds **6**.

The different course of the reaction can probably be explained by the formation of an intermediate (**8**), which reacts with malononitrile to give finally the spiro-4,4′-piperidinopyrano[2,3-*c*]pyrazoles, **6** (Scheme 3).

That the first version of the reaction (Scheme 1) is important is favored by the fact that dimers **4** (3–4% according to $^1$H NMR spectroscopy) are formed along with the compounds **6**. Compounds **6** were obtained in pure form after recrystallization from ethanol.

To study this reaction, we introduced the model cage compound, adamantan-2-one (**9**, Scheme 4) into the described three-component condensation instead of the piperidin-4-ones. In our opinion, compound **9** introduces some steric hindrance to the formation of the spiro-4,4′-adamantanopyrano[2,3-*c*]pyrazole (**10**). In this case, the reaction occurs, in fact, to form the stable Michael adduct (**11**), which is not cyclized to pyran **10** upon prolonged refluxing in ethanol in the presence of triethylamine. This also favors, to a certain extent, the first version of the reaction (Scheme 1).

We have also studied the electrochemical version of the three-component condensation. It was found that the regioselectivity of the reaction was the same and the passage of current for a short time through the acetonitrile solution of **2**, **3** and **5** in the presence of $Bu_4NBr$ under nitrogen led to formation of compounds **6h–j** (method C). It should be




**Scheme 4.**

**Table 1**. Method and yield of substituted 1′-substituted 6-amino-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles-5-carbonitriles, **6a-j** as well as compounds **11** and **13a-b**

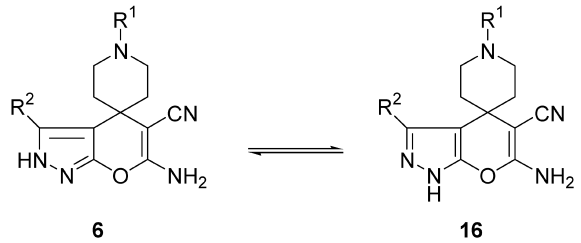
| Compound | Yield (%) | | | Electrolysis conditions, charge (C); current (mA) |
|---|---|---|---|---|
| | Method A | Method B | Method C | |
| **6a** | 89 | | | |
| **6b** | 58 | | | |
| **6c** | | 73 | | |
| **6d** | | 84 | | |
| **6e** | | 67 | | |
| **6f** | | 51 | | |
| **6g** | | 79 | | |
| **6h** | 78 | | 90 | 38; 3.8 |
| **6i** | 65 | | 79 | 43; 6.2 |
| **6j** | 64 | | 79 | 39; 4.8 |
| **11** | 90 | | | |
| **13a** | | 82 | | |
| **13b** | | 94 | | |

noted that the electrochemical process is more regioselective, the products of the reaction are analytically pure and do not require further recrystallization. Therefore the yield of final products **6** obtained electrochemically is ~12–15% higher than by Method A (Table 1).

Analogously, high regioselectivity has been observed earlier in the electrochemical synthesis of 2-amino-4-aryl-6-methyl-5-ethoxycarbonyl-4*H*-pyran-3-carbonitriles.[10] Probably such regioselectivity has been determined by the stringent reaction sequence (the initially formed unsaturated nitrile, **1**, reacts with the pyrazol-5-ones to give Michael adduct, **7**, then, intramolecular cyclization and tautomeric transformation lead to the desired product **6**).

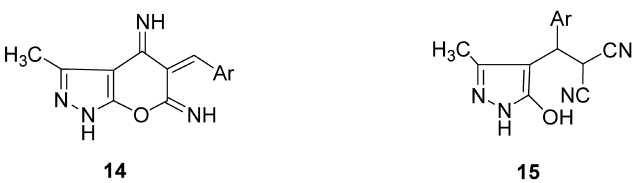
Various substituted pyrazolin-5-ones, piperidin-4-ones and their N and C-substituted analogs enter readily into this three-component condensation. *N*-Alkylpiperidin-4-ones act as catalysts due to their high basicity, and the reaction is autocatalytic. For example, the hydrochloride of compound **2b**, in the presence of excess triethylamine, gave the corresponding hydrochloride of compound **6**. Unlike compounds **2**, di- and trimethylpiperidin-4-ones (**12a**,**b**, Scheme 5) react in the three-component condensation to form the corresponding spiro-4,4′-piperidinopyrano[2,3-*c*]-pyrazoles (**13a**,**b**).

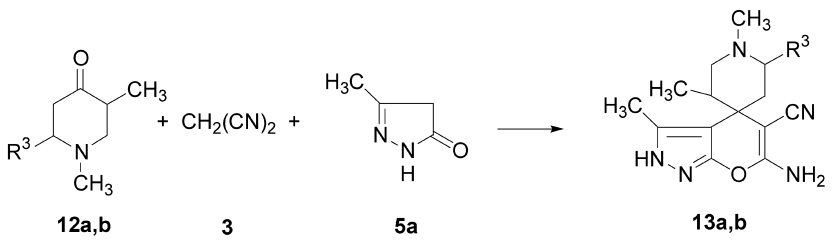
The structure of the synthesized spiro-4,4′-piperidinopyrano-[2,3-*c*]pyrazoles was compared to that of the previously known 4-arylpyranopyrazoles because for several years a uniform opinion concerning the structure of the condensation products of aromatic aldehydes, malononitrile, and pyrazolin-5-one has not been formulated. For example, the authors of reference 11 mistakenly ascribed the diimino-pyranopyrazole (**14**) structure to the products of this reaction.[11] It was shown later that this reaction proceeds through the Michael adduct (**15**), which is cyclized in the presence of bases to form the substituted 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles (**6**⇌**16**, Scheme 6).[3,12] However, the question about whether the hydrogen atom is positioned at the N(1) or N(2) atom of the pyranopyrazoles remains unclear, despite recent work.[13]



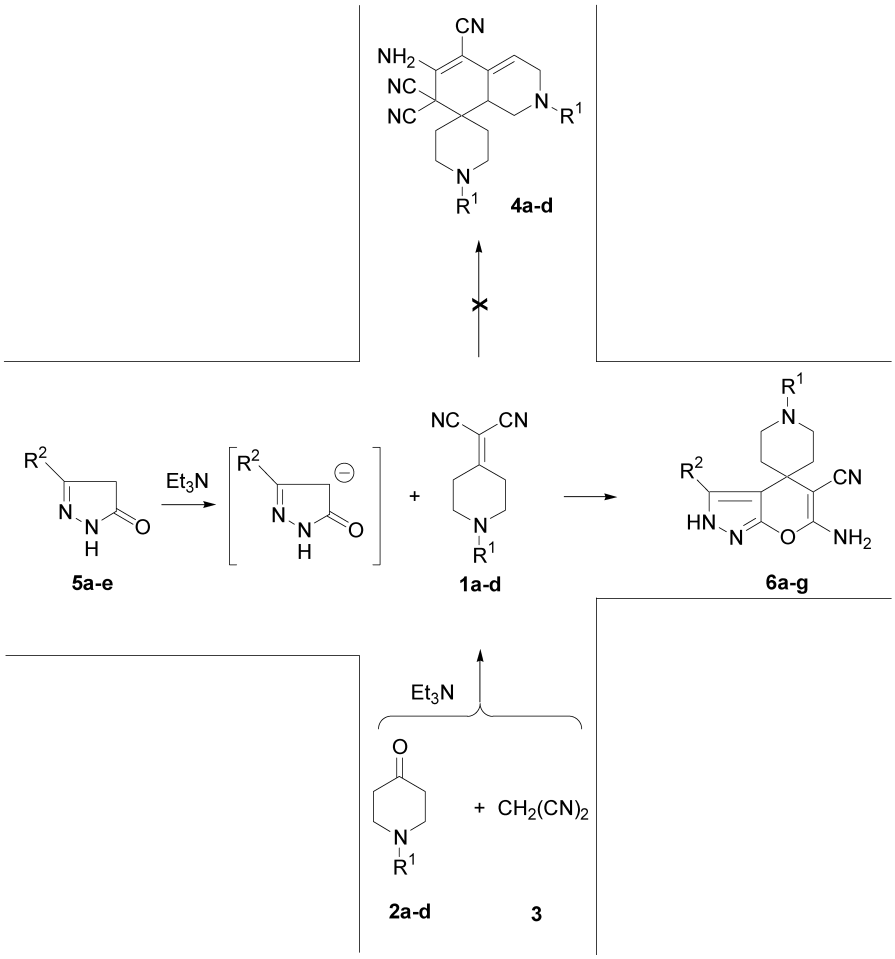

**Scheme 6.**

Based on the spectral data of the compounds (see Section 4) and comparison with the X-ray diffraction data for 6-amino-4-(2′,4′,6′-triethylphenyl)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile,[14] we chose structure **6** of the two alternative structures **6** and **16**.




**Scheme 5.** *Reagents and conditions*: **12a**, **13a** $R^3$=H; **12b**, **13b** $R^3$=$CH_3$.




**Scheme 7.**

## 3. Conclusion

Note in conclusion that the cross-condensation of carbonyl compounds (piperidin-4-ones and pyrazol-5-ones) with derivatives of cyanoacetic acid and malononitrile includes the simultaneous generation of a nucleophile (pyrazol-5-one anion) and an electrophile (piperidinylidenemalononitrile) under the action of a base in the reaction mixture (Scheme 7). The electrophile and nucleophile 'meet at the crossroads of the reaction' and interact.

Of course, the direction of the reaction and formation of either compound **4** or **6** depend on the structure of the intermediates and the conditions of their interaction, and it is difficult to predict the reaction direction unambiguously. The practical part of the study prevails at this stage. However, we can already say that the study of cross-condensations of this type is very important because it leads to the development of one-step methods for synthesis of complicated and interesting organic compounds.

## 4. Experimental

### 4.1. General

Melting temperatures were determined on a Kofler stage. IR spectra were recorded on Specord M-80 instrument for potassium bromide (1/200) pellets. $^{1}$H NMR spectra were measured on a Bruker AM-300 spectrometer (300 MHz) in DMSO-$D_6$ relative to tetramethylsilane. $^{13}$C NMR spectra were measured on a Bruker AC-200 spectrometer (50.32 MHz) and Bruker AM-300 spectrometer (75.47 MHz) in DMSO-$D_6$ relative to tetramethylsilane. Elemental analyses were carried out on a Perkin–Elmer C, H, N analyzer.

### 4.2. General procedures for the synthesis of 1′-substituted 6-amino-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano-[2,3-*c*]pyrazoles-5-carbonitriles, 6, as well as compounds 11 and 13

*Method A*. A solution of the corresponding ketone **2**, **9** or **12** (10 mmol), malononitrile **3** (10 mmol), and pyrazol-5-one **5** (10 mmol) and 0.5 mL of triethylamine in absolute ethanol (25 mL) was refluxed for 10 min. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from acetonitrile or ethanol.

*Method B*. A solution of the corresponding ketone **2**, **9** or **12** (10 mmol), malononitrile **3** (10 mmol), and pyrazol-5-one **5** (10 mmol) (in the case of compounds **2b** and **9**, 0.5 mL of triethylamine was also added) in absolute ethanol (25 mL) was stirred for 12 h at room temperature. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from acetonitrile or ethanol.

*Method C*. The cell for the electrolysis was an 80-mL glass beaker with a polyethylene cover into which were fitted the anode compartment which was surrounded by a cylindrically-shaped platinum gauze cathode (ca. 20 $cm^2$). The anode compartment was a polyethylene tube, about 2 cm in diameter, into which the magnesium anode (6-mm diameter rod) was fitted through a pierced septum. About 30 holes (5 mm) were drilled through the side of the tube, which was then wrapped with three layers of tracing paper to serve as separator between the anode and cathode compartments.

The catholyte was 40 mL of 0.10 M $Bu_4NBr$ in acetonitrile containing 10 mmol each of **2e**,**f**, **3** and **5c**,**e**. The anode compartment held about 20 mL of electrolyte. The electrolyses were carried out under controlled current conditions (see Table 1) in the vigorously stirred, nitrogen-purged catholyte. After passing the specified amount of charge (Table 1), the solvent was removed from the catholyte with a rotary evaporator. The residue was taken up in ethanol (ca. 20 mL) and the product was precipitated by addition of 5–10 mL of water. The precipitate was filtered off and washed with ethanol to give **6h**–**j**. No purification was required.

**4.2.1. 6-Amino-3-methyl-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile hydrochloride (6a).** Mp 268°C. [Found: C 51.11; H 5.84; N 24.83; $C_{12}H_{15}N_5O{\cdot}HCl$ requires C 51.16; H 5.73; N 24.86%]; $\nu_{max}$ (KBr) 3400, 3095, 2190, 1626 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.12 (br s, 1H), 9.34 (br s, 2H), 6.86 (s, 2H), 3.55 (m, 2H), 3.30 (m, 2H), 2.48 (m, 2H), 2.40 (s, 3H), 1.92 (m, 2H). $\delta_C$ (50.32 MHz, DMSO-$D_6$) 162.34, 154.16, 135.12, 124.74, 113.68, 101.49, 89.09, 57.75, 40.47, 35.68, 30.13, 11.66.

**4.2.2. 6-Amino-3-ethyl-spiro-4-(piperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile hydrochloride (6b).** Mp 198–199°C. [Found: C 52.87; H 6.20; N 23.64; $C_{13}H_{17}N_5O{\cdot}HCl$: requires C 52.80; H 6.13; N 23.68%]; $\nu_{max}$ (KBr) 3410, 3098, 2195, 1628 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.08 (s, 1H), 9.99 (br s, 1H), 9.18 (br s, 1H), 6.64 (s, 2H), 3.63 (m, 2H), 3.28 (d, 2H, *J*=13.1 Hz), 2.89 (q, 2H, *J*=7.1 Hz), 2.49 (m, 2H), 1.95 (d, 2H, *J*=14.4 Hz), 1.21 (t, 3H, *J*=7.5 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 162.21, 153.74, 142.85, 124.15, 114.45, 100.86, 95.62, 57.60, 40.26, 37.12, 30.29, 18.69, 13.93.

**4.2.3. 6-Amino-3-methyl-spiro-4-(*N*-methylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6c).** Mp 153–155°C. [Found: C 60.21; H 6.57; N 27.08; $C_{13}H_{17}N_5O$ requires C 60.22; H 6.61; N 27.01%]; $\nu_{max}$ IR (KBr) 3392, 3228, 3078, 2193, 1656 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 11.97 (br s, 1H), 6.50 (s, 2H), 2.72 (m, 2H), 2.63 (m, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 2.12 (m, 2H), 1.80 (m, 2H). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 161.84, 153.87, 142.64, 124.75, 112.92, 87.14, 49.86, 48.24, 39.18, 31.83, 11.67.

**4.2.4. 6-Amino-3-methyl-spiro-4-(*N*-ethylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6d).** Mp 166–168°C. [Found: C 61.37; H 6.97; N 25.68; $C_{14}H_{19}N_5O$ requires C 61.52; H 7.01; N 25.62%]; $\nu_{max}$ (KBr) 3390, 3315, 3200, 2196, 1648 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 11.87 (br s, 1H), 6.27 (s, 2H), 2.84 (m, 2H), 2.68 (m, 2H), 2.48 (q, 2H, *J*=7.1 Hz), 2.32 (s, 3H), 2.12 (m, 2H), 1.78 (m, 2H), 1.08 (t, 3H, *J*=7.1 Hz). $\delta_C$ (50.32 MHz, DMSO-$D_6$) 161.77, 154.46, 134.19, 123.87, 113.38, 102.85, 88.87, 51.66, 48.32, 40.28, 31.17, 12.00, 11.66.

**4.2.5. 6-Amino-3-methoxymethyl-spiro-4-(*N*-methylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6e).** Mp 170–172°C. [Found: C 58.20; H 6.57; N 24.29; $C_{14}H_{19}N_5O_2$ requires C 58.12; H 6.62; N 24.20%]; $\nu_{max}$ (KBr) 3394, 3225, 3095, 2194, 1653 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.33 (br s, 1H), 6.44 (s, 2H), 4.45 (s, 2H), 3.34 (s, 3H), 2.82 (t, 2H, *J*=10.5 Hz), 2.60 (m, 2H), 2.24 (s, 3H), 2.14 (m, 2H), 1.80 (d, 2H, *J*=13.1 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 160.20, 153.72, 134.82, 123.78, 113.38, 88.84, 65.35, 57.18, 54.07, 51.80, 45.66, 35.59, 34.12.

**4.2.6. 6-Amino-3-phenyl-spiro-4-(*N*-methylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6f).** Mp 179–172°C. [Found: C 67.16; H 5.98; N 21.93; $C_{18}H_{19}N_5O$ requires C 67.27; H 5.96; N 21.79%]; $\nu_{max}$ (KBr) 3385, 3220, 3126, 2190, 1649 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.40 (br s, 1H), 7.30–7.55 (m, 5H), 6.70 (s, 2H), 2.63 (m, 2H), 2.38 (m, 2H), 2.15 (s, 3H), 2.07 (m, 2H), 1.73 (d, 2H, *J*=14.0 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 160.89, 153.65, 130.80, 128.41, 127.59, 124.63, 113.19, 86.77, 53.81, 50.96, 45.30, 40.28, 35.57.

**4.2.7. 6-Amino-3-methyl-spiro-4-(*N*-phenethylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6g).** Mp 146–147°C. [Found: C 68.92; H 6.78; N 20.02; $C_{20}H_{23}N_5O$ requires C 68.75; H 6.63; N 20.04%]; $\nu_{max}$ (KBr) 3374, 3228, 3115, 2195, 1650 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 11.98 (br s, 1H), 7.14 (m, 5H), 6.50 (s, 2H), 2.94 (m, 2H), 2.80 (m, 2H), 2.78 (m, 2H), 2.68 (m, 2H), 2.28 (s, 3H), 2.10 (m, 2H), 1.78 (d, 2H, *J*=14.4 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 161.68, 154.32, 140.31, 134.16, 128.55, 128.10, 125.70, 123.92, 113.26, 102.72, 59.90, 49.49, 40.71, 38.59, 32.59, 30.97, 11.72.

**4.2.8. 6-Amino-3-methoxymethyl-spiro-4-(*N*-acetylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6h).** Mp 176–177°C. [Found: C 56.42; H 5.73; N 21.72; $C_{15}H_{19}N_5O_3$ requires C 56.77; H 6.03; N 22.07%]; $\nu_{max}$ (KBr) 3392, 3317, 3200, 2196, 1672, 1642 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.56 (s, 1H), 6.87 (s, 2H), 4.36 (s, 2H), 4.22 (m, 1H), 3.86 (m, 1H), 3.73 (m, 1H), 3.42 (m, 1H), 3.18 (s, 3H), 2.26 (s, 3H), 1.80–2.04 (m, 4H). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 168.75, 161.43, 153.74, 138.37, 123.40, 103.96, 61.74, 60.07, 59.03, 43.16, 32.16, 21.65 (the signal of C-4 carbon atom is overlapped with the signal for the carbon of DMSO).

**4.2.9. 6-Amino-3-(*n*-propyl)-spiro-4-(*N*-acetylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6i).** Mp 199–200°C. [Found: C 60.71; H 6.43; N 21.80; $C_{16}H_{21}N_5O_2$ requires C 60.94; H 6.71; N 22.20%]; $\nu_{max}$ (KBr) 3385, 3312, 3196, 2192, 1668, 1638 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.15 (s, 1H), 6.81 (s, 2H), 4.21 (m, 1H), 3.73 (m, 2H), 3.39 (m, 1H), 2.02 (s, 3H), 1.97 (m, 2H), 1.87 (m, 2H), 1.80–1.82 (m, 4H), 0.88 (t, 3H, *J*=7.0 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 168.51, 161.76, 153.98, 138.50, 123.43, 102.33, 59.53, 42.35, 37.66, 31.48, 27.43, 21.84, 21.32, 13.69.

**4.2.10. 6-Amino-3-methoxymethyl-spiro-4-(*N*-ethoxycarbonylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (6j).** Mp 157–160°C. [Found: C 55.07; H 5.82; N 19.73; $C_{16}H_{21}N_5O_4$ requires C 55.32; H 6.09; N 20.16%]; $\nu_{max}$ (KBr) 3390, 3316, 3204, 2197, 1684, 1640 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.40 (s, 1H), 6.62 (s, 2H), 4.38 (s, 2H), 4.08 (q, 2H, $J$=7.0 Hz), 3.88 (m, 2H), 3.62 (m, 2H), 3.28 (s, 3H), 2.07 (m, 2H), 1.74 (m, 2H), 1.24 (t, 3H, $J$=7.0 Hz). $\delta_C$ (75.47 MHz, DMSO-$D_6$) 161.71, 154.90, 154.39, 134.85, 123.13, 104.31, 90.55, 64.41, 60.60, 59.39, 57.49, 31.53, 14.55 (the signal of C-4 carbon atom is overlapped with the signal for the carbon of DMSO).

**4.2.11. 2-[2-(3-Hydroxy-5-methyl-1*H*-pyrazol-4-yl)-adamantan-2-yl]-malononitrile (11).** Mp 190°C. [Found: C 69.08; H 7.03; N 18.72; $C_{17}H_{20}N_4O$ requires C 68.89; H 6.80; N 18.90%]; $\nu_{max}$ (KBr) 2228, 1590 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 10.08 (br s, 1H), 5.20 (s, 1H), 3.16 (s, 1H), 1.88–2.11 (m, 17H). $\delta_C$ (50.32 MHz, DMSO-$D_6$) 160.90, 139.40, 111.87, 88.87, 40.84–38.34 (signals are overlapped with the signal for the carbon of DMSO), 35.24, 26.67, 11.12.

**4.2.12. 6-Amino-3-methyl-spiro-4-(1′,3′-dimethylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (13a).** Mp 204–205°C. [Found: C 61.50; H 7.08; N 25.63; $C_{14}H_{19}N_5O$ requires C 61.52; H 7.01; N 25.62%]; $\nu_{max}$ (KBr) 3248, 3125, 2184, 1656, 1600 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 11.90 (m, 1H), 6.37 (s, 2H), 2.90 (m, 2H), 2.75 (m, 1H), 2.49 (m, 3H), 2.25 (s, 3H), 2.18 (s, 1H), 2.12 (m, 2H),1.84 (d, 1H, $J$=6.8 Hz), 0.70 (d, 3H, $J$=6.8 Hz). $\delta_C$ (50.32 MHz, DMSO-$D_6$) 163.02, 155.32, 133.79, 124.08, 100.96, 88.91, 57.23, 54.83, 50.71, 45.42, 35.41, 14.40, 11.35 (the signal of C-4 carbon atom is overlapped with the signal for the carbon of DMSO).

**4.2.13. 6-Amino-3-methyl-spiro-4-(1′,2′,5′-trimethylpiperidine-4′)-2*H*,4*H*-pyrano[2,3-*c*]pyrazole-5-carbonitrile (13b).** Mp 210–212°C. [Found: C 62.62; H 7.28; N 24.26; $C_{15}H_{21}N_5O$ requires C 62.70; H 7.37; N 24.37%]; $\nu_{max}$ (KBr) 3288, 3120, 2176, 1632, 1600 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO-$D_6$) 12.00 (br s, 1H), 6.54 (br s, 2H), 2.90 (m, 1H), 2.48–2.72 (m, 2H), 2.22 (s, 3H), 2.21 (s, 3H), 2.10 (m, 1H), 1.79 (m, 2H), 0.99 (d, 3H, $J$=5.6 Hz), 0.64 (d, 3H, $J$=6.2 Hz). $\delta_C$ (50.32 MHz, DMSO-$D_6$) 162.71, 154.95, 133.44, 123.75, 100.68, 58.55, 55.61, 53.09, 48.50, 41.81, 36.94, 20.12, 13.94, 11.21 (the signal of C-4 carbon atom is overlapped with the signal for the carbon of DMSO).

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