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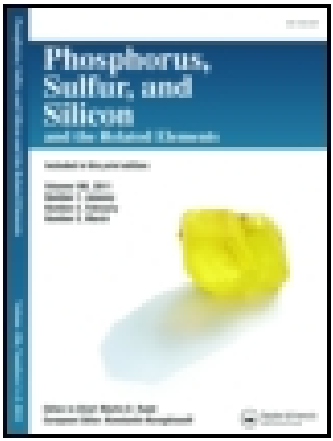

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One-Step Synthesis of Substituted 3,5-Dicyanospiro-4-(piperidine-4′)-1H,4H-dihydropyridine-2-thiolates and 2,6-Diamino-3,5-dicyanospiro-4-[(piperidine-4′) or (2′-oxoindole-3′)]-4H-thiopyrans

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One-Step Synthesis of Substituted 3,5-Dicyanospiro-4-(piperidine-4′)-1*H*,4*H*-dihydropyridine-2-thiolates and 2,6-Diamino-3,5-dicyanospiro-4-[(piperidine-4′) or (2′-oxoindole-3′)]-4*H*-thiopyrans

Anatoliy M. Shestopalov, Alexander A. Shestopalov, Lyudmila A. Rodinovskaya, and Anna V. Gromova
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A new, one-step method for the synthesis of substituted 3,5-dicyanospiro-4-(piperidine-4′)-1H,4H-dihydropyridine-3-thiolates and 2,6-diamino-3,5-dicyanospiro-4-[(piperidine-4′) or (2′-oxoindole-3′)]-4H-thiopyrans using a multicomponent reaction of N-substituted piperidine-4-ones and isatins with derivatives of cyanoacetic acid is described. The regioselectivity of this reaction can be controlled by varying the substituents at the nitrogen atom of the piperidine-4-ones. The multicomponent reaction of N-alkylpiperidine-4-ones with malononitrile and cyanothioacetamide gives spiro-4-(1′-alkylpiperidine-4′)-1H,4H-dihydropyridine-2-thiolates, whereas a similar reaction of N-(acyl)alkoxycarbonylpiperidine-4-ones leads exclusively to spiro-4-(1′-(acyl)alkoxycarbonylpiperidine-4′)-4H-thiopyrans.

Keywords Cyanothioacetamide; malononitrile; multicomponent reaction; spiroheterocycles; thiopyrans

INTRODUCTION

Substituted 3,5-dicyano-pyridine-2-(thiones)thioles are known substrates for biologically active compounds.[1] Among them are compounds acting as adenosine (A1) agonists,[2] vasodilators,[3] antianginal preparates,[4] and inhibitors of the prion replication.[5] Most methods for their synthesis are based on laborious procedures, which often

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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include two or three separate steps. Usually an unsaturated nitrile or thioamide is prepared first, which is then reacted with cyanothioacetamide or malononitrile to produce the desired heterocycle.[6–8] 6-Amino-4-aryl-3,5-dicyanopyridine-2-(thiones)thioles are typically prepared by the reaction of arylidene-malononitriles or arylidenecyanothioacetamides with cyanothioacetamide or malononitrile in refluxing ethanol in the presence of *N*-methylmorpholine as a catalyst.[1,5–8] Alternatively, these compounds can be obtained by recyclization of 4-aryl-2,6-diamino-3,5-dicyano-4*H*-thiopyrans in refluxing ethanol in the presence of alkaline catalysts.[7,8] It also has been demonstrated that the described stepwise method can be applied for the synthesis of spiro-conjugated molecules; for example 6-amino-3,5-dicyanospirocyclohexan-1,4-dihydropyridine-2-thiole was prepared from cyclohexylidenemalononitrile and cyanothioacetamide.[9] Here we report a multicomponent reaction of *N*-substituted piperidin-4-ones with malononitrile and cyanothioacetamide. We have discovered that the regioselectivity of this reaction depends on the nature of the substituent at the nitrogen atom of the piperidine-4-one ring, and can be easily controlled just by varying the starting materials. Based on this discovery, we have developed regioselective multicomponent methods for the synthesis of novel 1,4-dihydropyridines and 4*H*-thiopyrans spiroconjugated with heterocycles.

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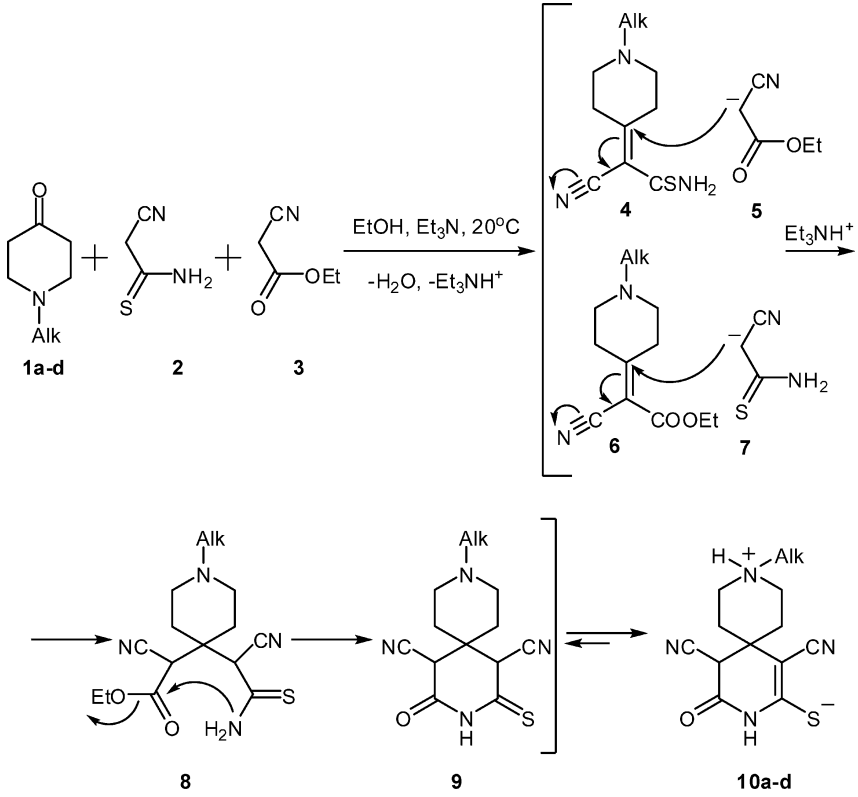
RESULTS AND DISCUSSION

N-Alkylpiperidine-4-ones **1** were reacted with cyanothioacetamide (**2**) and cyanoacetic ester **3** in ethanol in the presence of triethylamine at room temperature to give substituted spiro-piperidinepyridines **10a–d** with 92–95% yields. Most likely, the first step of this process is the simultaneous formation of electrophiles (unsaturated nitriles **4** or **6**) and nucleophiles **5** or **7**, which then react with each other in a Michael addition and form adduct **8**. The subsequent 1,6-elimination of ethanol from the Michael adduct leads to the formation of pyridine ring **9** (Scheme 1). According to the ^{1}H NMR spectra in DMSO-d_6, the heterocycles obtained exist in the betaine form **10**; a similar phenomenon was previously observed for the hydrogenated 4-pyridylpyridine-2(1*H*)-thiones and pyridoquinuclidine-2(1*H*)-thiones, when the basic pyridine and quinuclidine rings acted as proton acceptors.[1,10,11]

The formation of the betaine structures **10** suggests that the *N*-alkylpiperidine ring is basic enough to autocatalyze the described reaction. In our experiments, we did not observe the formation of pyridine-2-(1*H*)-thione salts with triethylamine, which is characteristic for other



1, **10** Alk = Et (a), Me (b), n-Pr (c), i-Pr (d).

SCHEME 1

hydrogenated pyridine-2(1*H*)-thiones,[12] probably due to the higher basicity of the piperidine cycle compared to that of triethylamine. Accordingly, we have prepared compounds **10a–d** from the same starting materials in ethanol at room temperature without adding triethylamine with 90–92% yields.

Contrary to the described reaction, *N*-acetyl and *N*-ethoxycarbonyl piperidine-4-ones **11a,b**, which lack basicity at the nitrogen atom, react with cyanothioacetamide (**2**) and cyanoacetic ester **3** only in the presence of an excess of *N*-methylmorpholine and form spiro-piperidine-pyridinethiolate salts **12a**,**b** (Scheme 2). In this reaction, an excess of *N*-methylmorpholine was used to drive the final pyridines into the heterogeneous phase and to increase their yields. A similar salification

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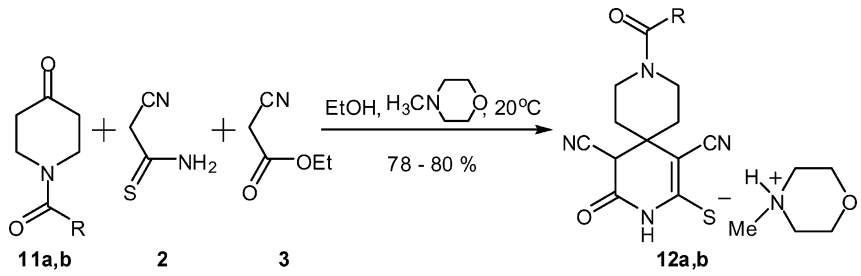

11,**12**: R = Me (**a**), EtO (**b**).

SCHEME 2

method was used previously to isolate hydrogentated pyridine-2(1*H*)-thiones.[1,12]

To further extend the spectrum of the compounds accessible by this multicomponent reaction, we have substituted cyanoacetic ester (**3**) for malononitrile (**13**). A three-component condensation of *N*-alkylpiperidine-4-ones **1a–e**, cyanothioacetamide, and malononitrile in ethanol at room temperature leads to 6-amino-spiropiperidinethiolates **14a-e** in 75–92% yields (Scheme 3, method A). This reaction proceeds without an alkaline catalyst, which suggests that it is autocatalyzed by the *N*-alkylpiperidine-4-ones. This notion is partially supported by the betaine structures of compounds **14**.

The same compounds **14a,b,e** were obtained by the reaction of two equivalents of cyanothioacetamide with corresponding *N*-alkylpiperidine-4-ones **1a,b,e** in 84–87% yields (Scheme 3, method B). However, this method does not have any preparative value, since first cyanothioacetamide is prepared from malononitrile and hydrogen sulfide, and then hydrogen sulfide is eliminated in the course of the multicomponent condensation from one of the cyanothioacetamide molecules. Therefore, it is more advantageous to synthesize compounds **14a–e** directly from malononitrile and cyanothioacetamide.

Surprisingly, when *N*-acetyl and *N*-ethoxycarbonylpiperidine-4-ones **11a–c** were used in the condensation with cyanothioacetamide and malononitrile, the regioselectivity of the reaction was changed. Accordingly, the three-component condensation of **11a–c** with cyanothioacetamide and malononitrile in the presence of *N*-methylmorpholine in ethanol at room temperature produced 2,6-diamino-3,5-dicyano-4*H*-spiropiperidinethiopyrans **15** instead of the expected pyridines **14** (Scheme 4).

Compounds **15** were much more stable than their 4-aryl-substituted analogs,[7,8] and they did not undergo recyclization into

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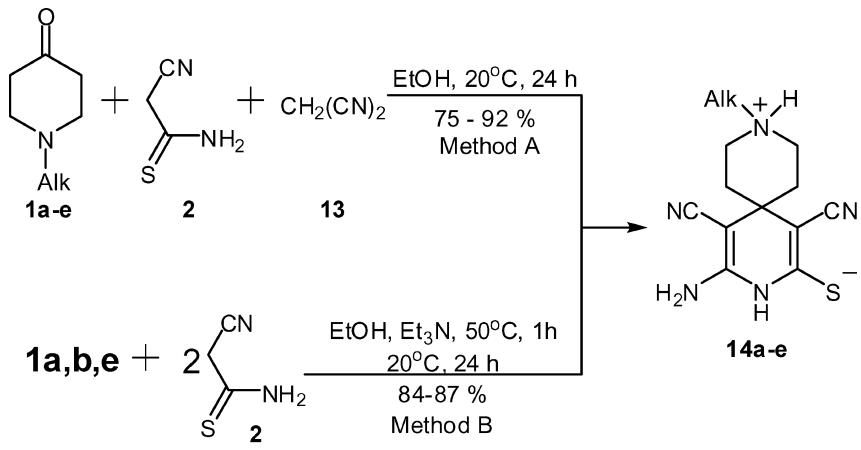
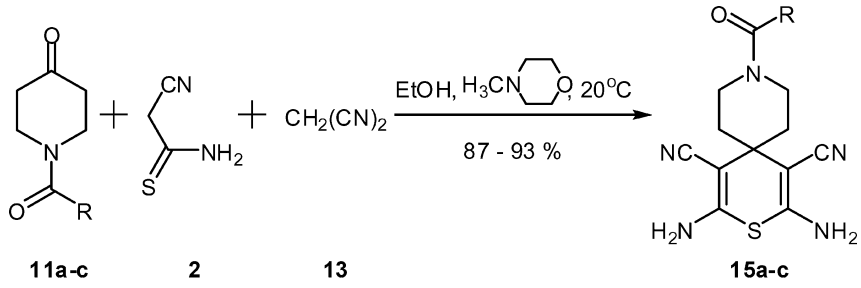


1, **14**: Alk = Et (**a**), Me (**b**), n-Pr (**c**), i-Pr (**d**), C6H5CH2 (**e**).

SCHEME 3



11, **15**: R = Me (**a**), EtO (**b**), t-BuO (**c**).

SCHEME 4

6-aminopyridines **14** even after refluxing in ethanol or after heating in DMSO at 100–110°C in the presence of *N*-methylmorpholine.

The structures and purities of compounds **10–15** were supported by elemental analysis, and by IR and NMR spectroscopy (Table I). In the IR spectra, betaines **10** and **14** show characteristic weak (shoulder) wide bands for the NH and NH_2 groups at 3100–3400 cm^{-1}.[1,12–14] The ^1H NMR spectra of compounds **10–15** contain signals for the spiro-conjugated piperidine ring in addition to the signals of the NH and NH_2 groups (Table I). The resonance peaks of the N^+H protons in the ^1H NMR spectra of betaines **10** and **14** appear at 9.1–9.4 ppm as broad singlets (Table I), while the spectra of **12** and **15** do not show such

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TABLE I Physicochemical and Spectral Properties of Compounds 10, 12, 14, 15, and 20

	Yield, % (Me-thod)	mp,°C	Found / Calculated, % C	H	N	Formula	IR spectra, ν, cm^{-1}	H^1 NMR spectra, δ ppm, ^3J Hz
10a	93	284–286	56.32 56.50	5.79 5.84	20.31 20.27	$C_{13}H_{16}N_4OS$	1647 (CONH); 2195, 2212 (CN); 3206, 3380, 3410 (NH, N^+H)	0.94 (t, $J = 7.3$, 3H, CH_3); 1.85 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 2.19 (q, $J = 7.3$, 2H, CH_2N); 3.20 (m, 2H, $C^{2'}H_2$); 3.38 (m, 2H, $C^{6'}H_2$); 4.45 (s, 1H, C^5H); 9.08 (br. s., 1H, N^+H); 9.70 (s, 1H, NH).
10b	95	296–298	54.59 54.94	5.31 5.38	21.20 21.36	$C_{12}H_{14}N_4OS$	1642 (CONH); 2192, 2210 (CN); 3218, 3375, 3418 (NH, N^+H)	1.83 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 2.85 (s, 3H, CH_3); 3.20 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 4.37 (s, 1H, C^5H); 9.14 (br. s., 1H, N^+H); 9.18 (s, 1H, NH).
10c	92	276–278	57.84 57.91	6.17 6.25	18.95 19.29	$C_{14}H_{18}N_4OS$	1638 (CONH); 2196, 2205 (CN); 3210, 3368, 3420 (NH, N^+H)	0.94 (t, $J = 7.6$, 3H, CH_3); 1.68 (m, 2H, $\underline{CH_2}CH_3$); 1.92 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 3.02 (t, $J = 7.3$, 2H, CH_2N); 3.24 (m, 2H, $C^{2'}H_2$); 3.40 (m, 2H, $C^{6'}H_2$); 4.44 (s, 1H, C^5H); 9.08 (br. s., 1H, N^+H); 9.45 (s, 1H, NH).

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TABLE I Physicochemical and Spectral Properties of Compounds 10, 12, 14, 15, and 20 (*Continued*)

	Yield, % (Me-thod)	mp,°C	Found / Calculated, % C	H	N	Formula	IR spectra, ν, cm^{-1}	H^1 NMR spectra, δ ppm, ^3J Hz
10d	93	268–270	57.63 57.91	6.44 6.25	19.34 19.29	$C_{14}H_{18}N_4OS$	1636 (CONH); 2192, 2208 (CN); 3225, 3370, 3425 (NH, N^+H)	1.30 (d, $J = 7.4$, 6H, $(CH_3)_2$); 1.95 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.08 (m, 1H, CHN); 3.28 (m, 2H, $C^{2'}H_2$); 3.50 (m, 2H, $C^{6'}H_2$); 4.42 (s, 1H, C^5H); 9.08 (br. s., 1H, N^+H); 9.45 (s, 1H, NH).
12a	80	278–280	55.12 55.22	6.21 6.44	17.63 17.89	$C_{18}H_{25}N_5O_3S$	1632 (CONH); 1664 ($COCH_3$); 2190, 2210 (CN); 3340, 3480 (NH, N^+H)	1.50-1.82 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 2.02 (s, 3H, CH_3CO); 2.83 (s, 3H, CH_3N); 3.18 (m, 4H, CH_2NCH_2); 3.50-3.88 (m, 8H, $C^{2'}H_2$, $C^{6'}H_2$, CH_2OCH_2); 4.08 (s, 1H, C^5H); 9.28 (s, 1H, NH).
12b	78	264–266	54.37 54.14	6.41 6.46	16.74 16.61	$C_{19}H_{27}N_5O_4S$	1634 (CONH); 1685 (COOEt); 2196, 2196 (CN); 3338, 3483 (NH, N^+H)	1.21 (t, $J = 7.8$, 3H, $\underline{CH_3}CH_2$); 1.54-1.83 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 2.83 (s, 3H, CH_3N); 3.24 (m, 4H, CH_2NCH_2); 3.58 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 3.82 (m, 4H, CH_2OCH_2); 4.07 (s, 1H, C^5H); 4.11 (q, $J = 7.8$, 2H, CH_2O); 9.28 (s, 1H, NH).

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14a	90 (A) 84 (B)	289–291 (dec.)	56.84 56.70	6.51 6.22	25.19 25.43	$C_{13}H_{17}N_5S$	1642 (δ NH_2); 2192 (CN); 3310, 3405 (NH, NH_2)	1.23 (t, $J = 7.9$, 3H, CH_3); 1.92 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.08 (q, $J = 7.9$, 2H, CH_2N); 3.28 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 5.57 (s, 2H, NH_2); 8.26 (s, 1H, NH); 9.03 (br. s., 1H, N^+H).
14b	92 (A) 86 (B)	298–300 (dec.)	55.10 55.15	5.84 5.79	26.73 26.80	$C_{12}H_{15}N_5S$	1644 (δ NH_2); 2190 (CN); 3308, 3410 (NH, NH_2)	1.88 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 2.75 (s, 3H, CH_3); 3.87 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 5.56 (s, 2H, NH_2); 8.24 (s, 1H, NH); 9.05 (br. s., 1H, N^+H).
14c	85 (A)	271–273 (dec.)	57.83 58.10	6.57 6.62	24.31 24.20	$C_{14}H_{19}N_5S$	1640 (δ NH_2); 2185 (CN); 3312, 3400 (NH, NH_2)	0.97 (t, $J = 7.4$, 3H, CH_3); 1.73 (m, 2H, $\underline{CH_2}CH_3$); 1.88 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.02 (t, $J = 7.4$, 2H, NCH_2); 3.47 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 5.52 (s, 2H, NH_2); 8.26 (s, 1H, NH); 9.15 (br. s., 1H, N^+H).

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TABLE I Physicochemical and Spectral Properties of Compounds 10, 12, 14, 15, and 20 (*Continued*)

	Yield, % (Me-thod)	mp, °C	Found / Calculated, % C	H	N	Formula	IR spectra, ν, cm^{-1}	H^1 NMR spectra, δ ppm, ^3J Hz
14d	83 (A)	263–265	57.94 58.10	6.43 6.62	24.14 24.20	$C_{14}H_{19}N_5S$	1638 (δ NH_2); 2188 (CN); 3314, 3410 (NH, NH_2)	1.27 (d, $J = 7.9$, 6H, $(CH_3)_2$); 1.88 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.20 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 3.48 (m, 1H, CHN); 5.53 (s, 2H, NH_2); 8.22 (s, 1H, NH); 8.86 (br. s., 1H, N^+H).
14e	75 (A) 87 (B)	283–285 (dec.)	63.83 64.07	5.54 5.68	20.84 20.75	$C_{18}H_{19}N_5S$	1648 (δ NH_2); 2190 (CN); 3320, 3415 (NH, NH_2)	1.88 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.18 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 4.26 (s, 2H, $\underline{CH_2}C_6H_5$); 5.54 (s, 2H, NH_2); 7.48 (m, 5H, C_6H_5); 8.22 (s, 1H, NH); 9.42 (br. s., 1H, N^+H).
15a	90	258–259	54.23 53.96	5.19 5.23	24.01 24.20	$C_{13}H_{15}N_5OS$	1645 (δ NH_2); 1667 (CO); 2195 (CN); 3112, 3284, 3376 (NH_2)	1.74 (m, 2H, $C^{3'}H_2$); 1.85 (m, 2H, $C^{5'}H_2$); 2.03 (s, 3H, CH_3); 3.08 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 6.92 (s, 4H, $(NH_2)_2$).
15b	93	247–248	52.33 52.65	5.44 5.37	21.77 21.93	$C_{14}H_{17}N_5O_2S$	1644 (δ NH_2); 1685 (CO); 2198 (CN); 3126, 3276, 3385 (NH_2)	1.19 (t, $J = 7.8$ 3H, CH_3); 1.78 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.54 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 4.08 (q, $J =$ 7.8 2H, CH_2O); 6.83 (s, 4H, $(NH_2)_2$).

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15c	87	235–236	55.43 55.31	5.88 6.09	20.44 20.16	$C_{16}H_{21}N_5O_2S$	1640 (δ NH_2); 1678 (CO); 2195 (CN); 3134, 3278, 3380 (NH_2)	1.42 (s, 9H, *t*-Bu); 1.78 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 3.48 (m, 4H, $C^{2'}H_2$, $C^{6'}H_2$); 6.88 (s, 4H, $(NH_2)_2$).
20a	87	268–270 (dec.)	59.29 59.43	3.96 4.05	21.72 21.66	$C_{16}H_{13}N_5OS$	1647 ($CONH_2$, δ NH_2); 2182, 2195 (CN); 3227, 3340, 3428 (NH_2)	1.17 (t, $J = 7.7$, 3H, CH_3); 3.74 (q, $J = 7.7$, 2H, CH_2); 7.01 (br. s., 4H, $(NH_2)_2$); 7.08 (d, $J =$ 6.6, 1H, $C^{7'}H$); 7.10 (dd, $J = 8.0$, 6.6, 1H, $C^{6'}H$); 7.24 (d, $J = 6.7$, 1H, $C^{4'}H$); 7.34 (dd, $J = 8.0$, 6.7, 1H, $C^{5'}H$)
20b	90	287–285 (dec.)	46.18 46.40	2.51 2.60	18.17 18.04	$C_{15}H_{10}BrN_5OS$	1642 (CONH, δ NH_2); 2195 (br., CN); 3214, 3357, 3410 (NH_2)	3.16 (s, 3H, CH_3); 7.06 (d, $J = 8.6$, 1H, $C^{7'}H$), 7.11 (br. s., 4H, $(NH_2)_2$); 7.39 (d, $J = 1.9$, 1H, $C^{4'}H$); 7.55 (dd, $J = 8.6$, 1.9, 1H, $C^{6'}H$)

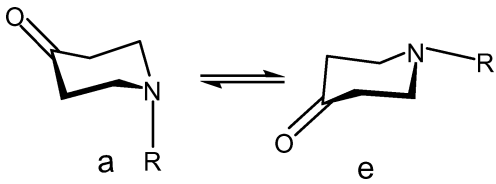

FIGURE 1

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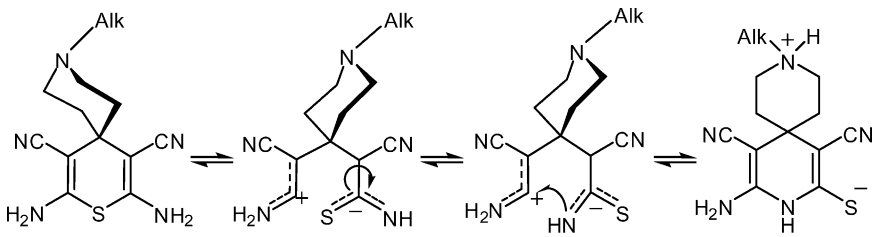
peaks. The N^+H proton of compounds **10** and **14** is very mobile and undergoes fast H/D-exchange in the presence of D_2O.

We assumed that the observed difference in the reactivities of *N*-substituted piperidine-4-ones **1** and **11** is governed by two factors: by the relative conformational stabilities of **1** and **11** and their corresponding intermediates, and by the high basicity of the piperidine ring, which can autocatalyze a recyclization of 2,6-diamino-3,5-dicyano-4*H*-thiopyrans into 6-amino-3,5-dicyanopyridine-2(1*H*)-thiones.[7,8]

N-alkylpiperidine-4-ones **1** adopt preferably the chair conformation and can undergo conformational transformation with equatorial-axial reorientation of the ring substituent (Figure 1).[13] However, the complete **a** ↔ **e** conversion requires inversion of all bonds in the piperidine ring. In *N*-acetyl and *N*-alkoxycarbonylpiperidine-4-ones **11**, the p-π conjugation of the N-C(O)-R fragment prohibits such bond inversions at the nitrogen atom, hinders conformational **a** ↔ **e** transformations, and results in the flattening of the piperidine ring. Moreover, solvolysis of the polar N-C(O)-R groups by the polar solvents further prohibits any transformation movements and fixes the substituent of the nitrogen atom in the equatorial position. Thus, acetyl and alkoxycarbonyl substituents in compounds **11** serve as conformational anchors and prevent any **a** ↔ **e** transformations.

Such conformational differences between **1** and **11** probably account for their different regioselectivities in the reactions with cyanothioacetamide and malononitrile. It is logical to assume that the reactions of *N*-alkylpiperidine-4-ones **1** with cyanothioacetamide and malononitrile also proceed through the formation of thiopyrans **15**. However, the conformational mobility of the *N*-alkylpiperidine ring and its high basicity result in subsequent recyclization of the thiopyrans into the more stable spiro-pyridines **14** just at room temperature (Scheme 5).

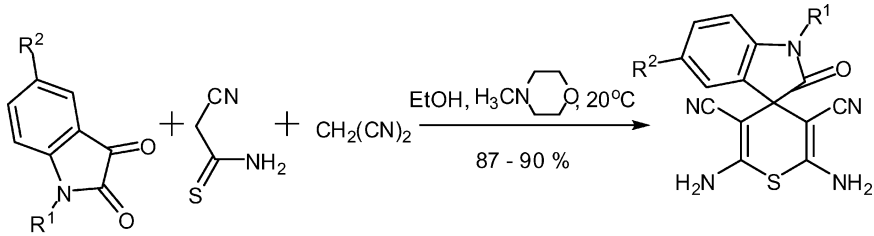
We have decided to support these assumptions by using a heterocyclic ketone, such as isatin, in this reaction, which is fixed in one conformation and cannot undergo any kind of transformational changes. Accordingly, a three-component condensation of isatins **19**, cyanothioacetamide, and malononitrile in ethanol at room



16 **17** **18** **14**

SCHEME 5

temperature in the presence of *N*-methylmorpholine produced the predicted 2,5-diamino-4*H*-spiro-(2-oxoindole)thiopyrans **20** in 87–90% yields (Scheme 6).



19a,b **2** **13** **20a,b**

19, **20**: R^1 = Et, R^2 = H (**a**); R^1 = Me, R^2 = Br (**b**).

SCHEME 6

Similarly to thiopyrans **15**, compounds **20** also were thermodynamically stable and did not undergo recyclization at 100–110°C in DMF in the presence of an alkaline catalyst. The structures of **20** were supported by elemental analysis and by IR and NMR spectroscopy (Table I). The ^{1}H NMR spectra of compounds **20** show the characteristic broad singlets of the NH_2 group in the 7.01–7.11 ppm region. The IR spectra of **20** display the high intensity absorption bands of the conjugated CN groups in the 2182–2195 cm^{-1}, as well as the characteristic bands of C(O)NR and NH_2 groups (Table I).

EXPERIMENTAL

Melting points were determined on a Kofler stage. Infrared spectra were obtained using a Perkin-Elmer 557 instrument in KBr pellets. ^{1}H NMR spectra were recorded using a Bruker AM-300 (300 MHz)

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spectrometer in DMSO-d_6 solutions. Elemental analysis was carried out with a Perkin-Elmer C, H, N analyzer.

Substituted 3,5-Dicyano-2-oxo-spiro-4-(piperidine-4′)-1,2,3,4-tetrahydro-pyridine-6-thiolates (10): General Procedure

A reaction mixture containing piperidin-4-one **1a–d** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), ethyl 2-cyanoacetate **3** (1.13 g, 10 mmol), and triethylamine (0.2 mL, 3 mmol) in ethanol (25 mL) was stirred at room temperature for 10 h. Then the reaction mixture was left at 4°C overnight. The precipitate formed was separated by filtration, washed with ethanol (2 × 5 mL) and petroleum ether (2 × 10 mL), and dried in an oven (5 h at 70°C) to give analytically pure compounds **10a–d** after recrystallization from nitromethane (Table I).

N-Methylmorpholine-3,5-dicyano-2-oxo-spiro-4-(piperidine-4′)-1,2,3,4-tetrahydropyridine-6-thiolates (12): General Procedure

A reaction mixture containing piperidin-4-one **11a,b** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), ethyl 2-cyanoacetate **3** (1.13 g, 10 mmol), and *N*-methylmorpholine (1.5 g, 15 mmol) in ethanol was stirred at room temperature for 2 h and then filtered. The filtrate was kept at 4°C for 3 days. The precipitate formed was separated by filtration, washed with ethanol (2 × 5 mL) and petroleum ether (2 × 10 mL), and dried in air. Compounds **12** were recrystallized from nitromethane (Table I).

Substituted 6-Amino-3,5-dicyano-spiro-4-(piperidine-4′)-1,4-dihidropyridine-2-thiolates (14): General Procedure

Method A

A reaction mixture containing piperidin-4-one **1** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), and malononitrile **13** (0.66 g, 10 mmol) in ethanol (25 mL) was stirred at room temperature for 2 h and then filtered. The filtrate was kept at 4°C for 3 days. The precipitate formed was separated by filtration, and washed with ethanol (2 × 5 mL) and petroleum ether (2 × 10 mL) to give analytically pure compounds **14a–e** after recrystallization from nitromethane (Table I).

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Method B

A reaction mixture containing the corresponding piperidin-4-one **1a,b,e** (10 mmol), cyanothioacetamide **2** (2.0 g, 20 mmol), and triethylamine (0.2 mL, 3 mmol) in ethanol (25 mL) was stirred at 50°C for 1 h (H_2S formation) and then filtered. The filtrate was kept at 4°C for 3 days. The precipitate formed was separated by filtration, and washed with ethanol (2 × 10 mL) and petroleum ether (2 × 5 mL) to give analytically pure compounds **14a,b,e** (Table I).

Substituted 2,6-Diamino-3,5-dicyano-spiro-4-(piperidine-4′)-4*H*-thiopyrans (15): General Procedure

A reaction mixture containing piperidin-4-one **11a-c** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), malononitrile **13** (0.66 g, 10 mmol), and triethylamine (0.2 mL, 3 mmol) in ethanol (20 mL) was stirred at room temperature for 1 h and then filtered. The filtrate was then kept at 4°C for 2 days. The precipitate formed was separated by filtration, and washed with ethanol (2 × 5 mL) and petroleum ether (2 × 10 mL) to give analytically pure compounds **15a–c** after recrystallization from isopropanol (Table I).

Substituted 2,6-Diamino-3,5-dicyano-spiro-4-(2′-oxoindol-3′)-4*H*-thiopyrans (20): General Procedure

To a stirring reaction mixture of isatin **19** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), and malononitrile **13** (0.66 g, 10 mmol) in ethanol (30 mL), *N*-methylmorpholine (0.2 mL) was added at room temperature. The reaction mixture was stirred at room temperature for an additional 6 h. The precipitate formed was separated by filtration, and washed with ethanol (2 × 10 mL) and petroleum ether (2 × 10 mL). Compounds **20a–c** were than recrystallized from a DMF:ethanol mixture (3:1) to give analytically pure samples (Table I).

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