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1-(Cyanoacetyl)-3,5-dimethylpyrazole as Active Methylene Compound in *Hantzsch*-type Pyridine Synthesis: A Convenient and Highly Effective Approach to 3,5-Dicyano-4-(het)aryl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates

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Summary. Reaction of 1-(cyanoacetyl)-3,5-dimethylpyrazole with (*E*)-2-cyano-3-(het)arylprop-2-enethioamides was used for the synthesis of *N*-methylmorpholinium 3,5-dicyano-4-(het)aryl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates for the first time. The latter were also obtained in a multicomponent one-pot mode *via* the condensation of cyanothioacetamide with corresponding aldehydes and above 1-cyanoacetylpyrazole in the presence of *N*-methylmorpholine under mild conditions. Thiolates **1** exist as a pair of *cis*/*trans*-diastereomers in different ratios (from 3:4 to 2:1).

Keywords. Heterocycles; Cyclizations; *Michael* addition; Pyridine-2-thiolates; Cyanoacetylpyrazole.

Introduction

In recent years, significant advances in the chemistry of 3-cyanopyridine-2(1*H*)-thiones and related compounds were achieved; this fact has resulted in a lot of papers and some detailed reviews [1]. Numerous examples demonstrating the useful properties of 3-cyanopyridine-2(1*H*)-thiones as well as its various applications in heterocyclic synthesis have been reported. Their partially hydrogenated derivatives, namely, 3-cyano-1,4-dihydro- and 1,4,5,6-tetrahydropyridine-2-thiolates, have not been subjected to detailed reactivity examination until now, but the chemistry of these compounds started to develop extensively only over the last decade [2]. During this period, we have investigated synthetic capabilities of partially hydrogenated pyridine-2-thiolates towards the synthesis of bispidine-type compounds and ring-fused 1,3,5-thiadiazines under *Mannich* reaction conditions [3]. Eventually, we found that some 3-cyanopyridine-2-thiolates may act as S,N-binucleophiles to afford pyrido[2,1-*b*][1,3,5]thiadiazines under mild aminomethylation with formaldehyde and primary amines [4], whereas those partially hydrogenated and bearing an electron-withdrawing moiety at C(5) rather reacted as C(3),C(5)-binucleophilic species to give diazabicyclo[3.3.1]nonane (*DABCN*, bispidine) derivatives [5–7]. Hence, our interest has been focused on the *Mannich*-derived synthesis of sulfur-containing bispidines – perspective chelating ligands to form complexes with transition metals and valuable pharmaceutical agents as well [8] starting from 3-cyanopyridine-2(1*H*)-thiones and corresponding thiolates. From this point our attention was attracted to the readily available 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1**, which are expected to be suitable predecessors of *DABCN* derivatives. In the preliminary communication [6], we presented some results on the aminomethylation of certain thiolates obtained so far.

General approaches to thiolates **1** are based on the *Hantzsch*-type cyclocondensation in the following

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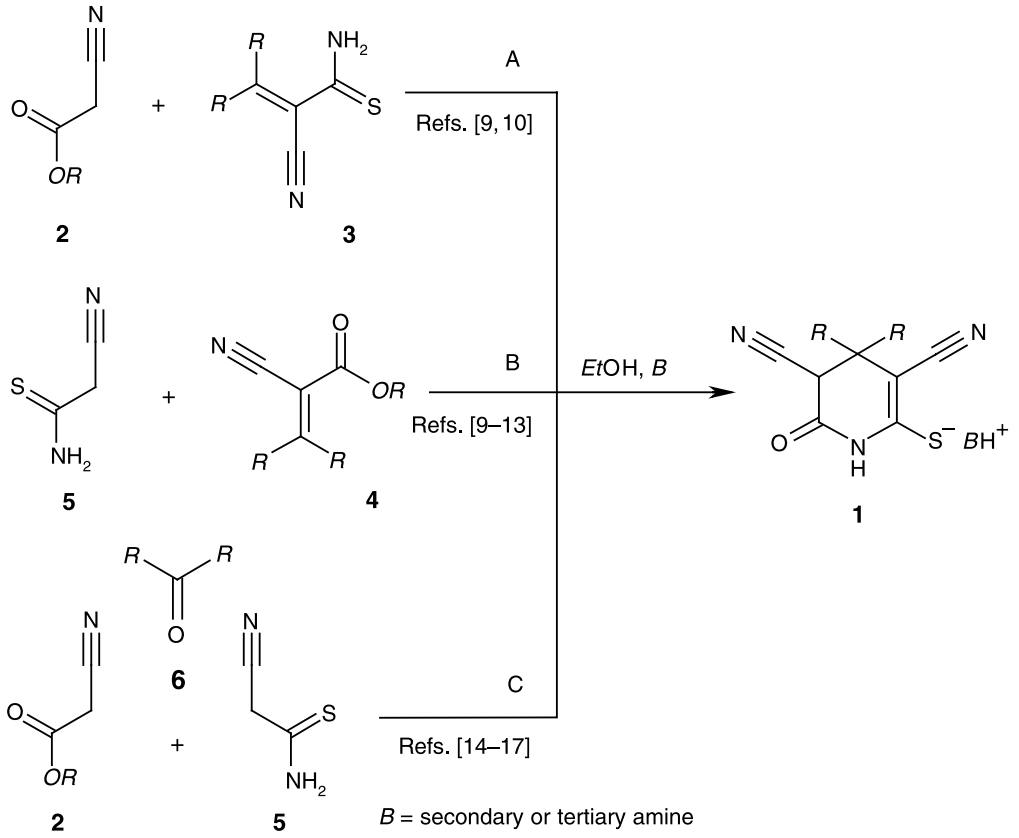
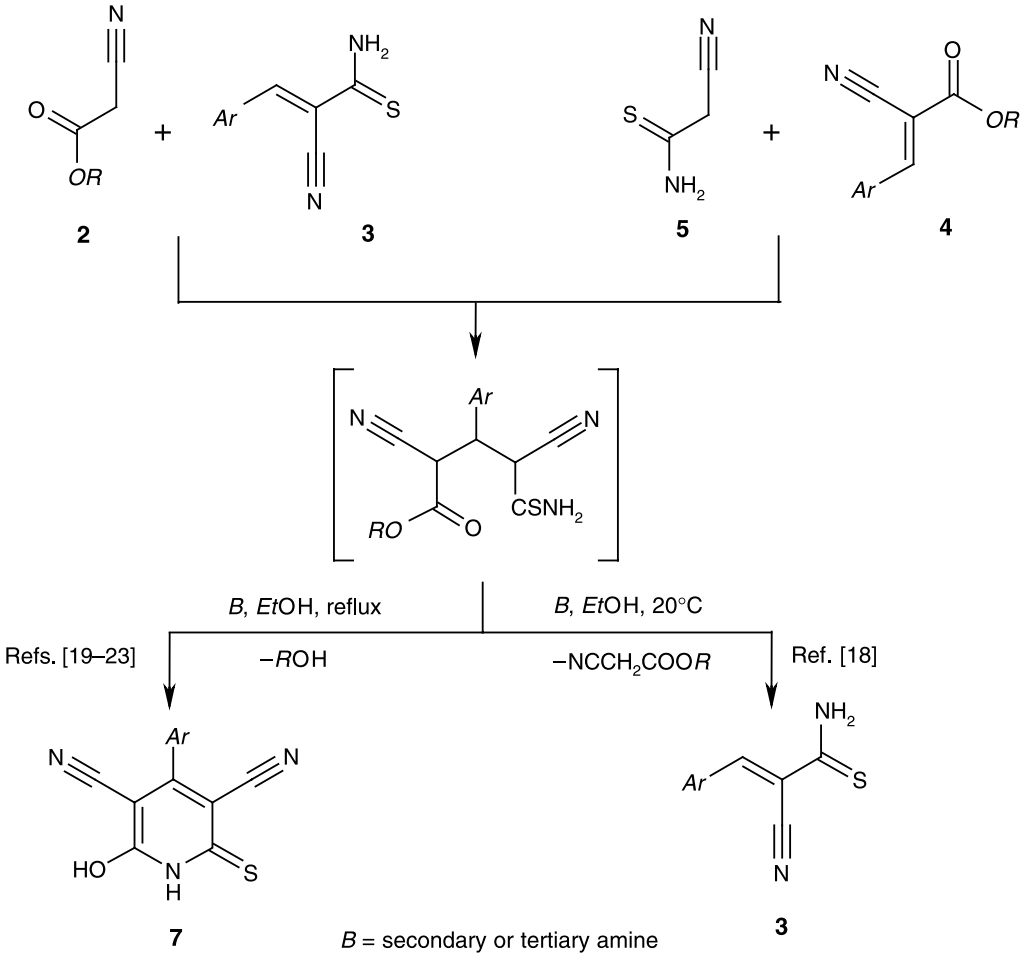


Scheme 1

modes: A) reaction of cyanoacetic esters **2** with 2-cyanoprop-2-enethioamides **3** [9, 10]; B) reaction of 2-cyanoacrylates **4** with cyanothioacetamide **5** [9–13]; or C) in a multicomponent way – on the reaction of corresponding aldehyde (ketone) **6**, esters **2**, and cyanothioacetamide **5** [14–17] (Scheme 1).

All the approaches suffer from some drawbacks. First, the yields of thiolates **1** are usually fair to good (40–80%), but sometimes these results are irreproducible for unknown reasons. Next, in most cases the reaction's course depends critically on the structure of starting compounds, sequence of mixing the components, as well as condensation conditions. Thus, in approach C satisfactory results were obtained when some aliphatic aldehydes, cycloalkanones, *Ph*CHO, and *ortho*-substituted benzaldehydes were used as carbonyl components **6** [15, 17]. However, in the case of aldehydes bearing strong electron-donating substituents (alkoxy-, dialkylamino-) at *para*/*ortho*-positions, only 3-aryl-2-cyanoprop-2-enethioamides **3** were isolated as the sole products as the result of so-called exchange of methylene components [17]. The same results were obtained when 3-aryl-2-cyanoacrylates **4** were treated with thioamide **5** in the presence of *N*-methylmorpholine at ambient temperature [18] (Scheme 2). Evidently, compounds **3** bearing strong electropositive groups in their 3-aryl substituent are less active in *Hantzsch* synthesis than other unsaturated thioamides, and do not react with cyanoacetic esters under mild conditions. Another limitation for the synthesis of 4-monosubstituted thiolates **1** is the side process of subsequent formation of 3,5-dicyano-6-hydroxypyridine-2(1*H*)-thiones **7** as by-products due to oxidation of thiolates **1** *in situ*. Compounds **7** became the main products when 3-aryl-2-cyanoprop-2-enethioamides **3** were put into reaction with cyanoacetates **2** under stronger conditions [19, 20]. Moreover, the reaction of 2-cyanoacrylates **4** with cyanothioacetamide **5**, which could be considered *a priori* as a contrary method for synthesis of **1** (Approach B), is also generally known as a method for synthesis of dehydrogenated pyridine-2(1*H*)-thiones **7** [19–23]. So, any methodology free from the drawbacks mentioned above and suited to selectively yield 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1** is of considerable inter-



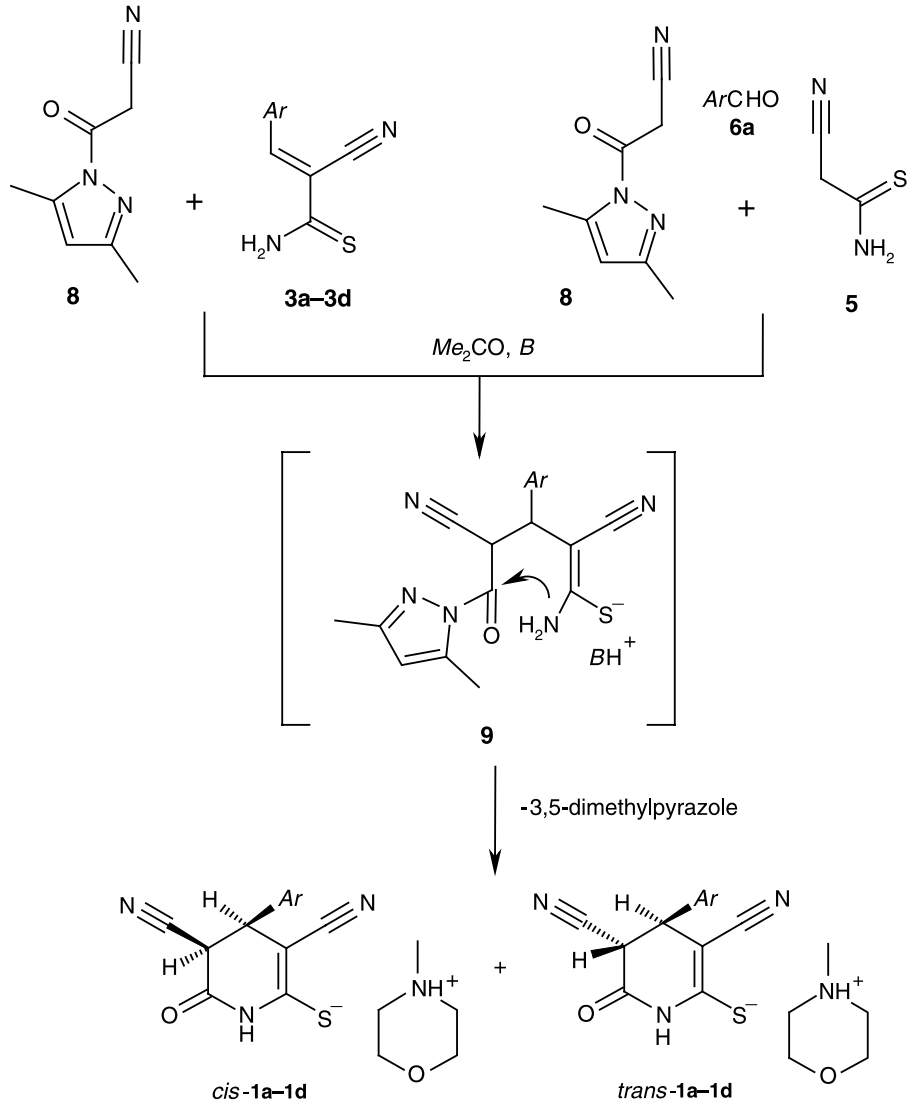
Scheme 2

est. Hence, we decided to put into the above *Hantzsch*-type reactions 1-cyanoacetyl-3,5-dimethylpyrazole (**8**) as active methylene component instead of cyanoacetic esters **2**.

Cyanoacetylpyrazole **8** is a very handy and cheap cyanoacetylation reagent, which was for the first time synthesized and introduced in common practice in late 1950s by *Ried et al.* [24–29]. It was successfully applied for the synthesis of various *N*-substituted cyanoacetamides and -hydrazides [25–28, 30–37], *N*-(cyanoacetyl)semicarbazides [32], (cyanoacetamido)phenyl acrylate polymers useful for making toners for electrostatographic developers [38], and found to be a good precursor for the generation of cyanoketene upon flash vacuum thermolysis [39]. Cyanoacetylpyrazole **8** in itself is known as an inhibitor of NH_4^+ to NO_3^- nitrification, thus preventing the nitrogen loss from the soil [40]. However, only few examples for use of this compound in heterocyclic chemistry have been reported up to now. Thus, when treated with phosgene or thiophosgene **8** yields mesomeric cross-conjugated betaines – anhydro-2-cyano-1-hydroxypyrazolo[1,2-*a*]pyrazolium hydroxides in poor yields (10%) [41]. Upon treatment with **8** in basic medium, 1,2,4-dithiazolium perchlorates undergo ring enlargement to produce 5-cyano-1,3-thiazin-6-ones [42], while 3,5-*bis*(2-oxocyclohexadienylidene)-1,2,4-dithiazolidine under similar conditions afforded 1-enzopyrano[3,4-*d*]pyrimidine derivatives [43]. Reaction with salicylaldehydes leading to 2-iminochromenes is the only known example featuring **8** in a *Knoevenagel*-type condensation [44]. However, **8** has never been used as an active methylene component in numerous modifications of *Hantzsch* pyridine synthesis [45].

Results and Discussion

We found that treatment of equimolar quantities of (*E*)-2-cyano-3-(het)arylprop-2-enethioamide **3a**–**3d**



Scheme 3

and **8** with 1.5 eq. of *N*-methylmorpholine in acetonic solution at 25°C gave *N*-methylmorpholinium 3,5-dicyano-4-(het)aryl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1a**–**1d** in good to excellent yields (68–96%) (Method A, Scheme 3). Thiolate **1a** was also obtained *via* a three-component one-pot condensation of *o*-chlorobenzaldehyde, cyanothioacetamide **5**, and **8** under similar conditions in 81% yield (Method B). We suggest that the reaction proceeds through a base-promoted *Michael* addition to form non-isolable adduct **9** followed by intramolecular *N*-acylation of the thiocarbamoyl moiety with elimination of 3,5-dimethylpyrazole.

All thiolates **1a**–**1d** were characterized by means of ^{1}H NMR measurements and IR spectra, as well as elemental analysis. As it followed from the ^{1}H NMR data, the reaction has a non-stereoselective character: all the obtained compounds in *DMSO*-d_6 solution exist as a mixture of two diastereomers in various ratios (from 3:4 to 2:1) with coupling constants $J_{C(4)H-C(5)H}$ of 6.3–7.3 and 9.7–11.4 Hz, corresponding to *cis*- and *trans*-isomers on basis of

torsional angle C(4)H–C(5)H calculations using the *Karplus-Conroy* equation (about 29–36 and 146–157°) [46]. This fact was found to be in good agreement with observations reported prior [15] for related pyridine-2-thiolates. As it follows from X-ray diffraction analysis data, (4*R*,5*S*)-structures (for **1b** and **1c** – (4*S*,5*S*)-structures) must be attributed to the *trans*-diastereomers of **1**; the latter were proven of being only *trans*-isomers in the solid state [15]. It is believed that the *cis*-isomers have a structure of (4*R*,5*R*)-diastereomers (for **1b** and **1c** – (4*S*,5*R*)-diastereomers). Probably, both stereomers appeared due to fast base-promoted C(5)-epimerization in *DMSO*-d_6 solution. Thus, two sets of protons were observed in the ^{1}H NMR spectra of **1a**–**1d**. Signals of C(4)H and C(5)H protons appeared as two doublets (or quartets, *AX*-system) at $\delta = 3.77$–4.91 ppm for *cis*-isomers and $\delta = 4.13$–4.45 ppm for *trans* ones with coupling constants values given above. Two broadened and partially deuterium-exchanged peaks at $\delta = 9.45$–9.71 ppm must be attributed to NH-protons. The IR spectra of thiolates **1** revealed the absorption bands in the regions 3180–3150 cm^{-1} (lactam NH stretches) and 1710–1680 cm^{-1} (lactam carbonyl stretching frequencies). For both conjugated ($\bar{\nu} = 2185$–2177 cm^{-1}, strong) and non-conjugated ($\bar{\nu} = 2253$–2247 cm^{-1}, weak) C≡N groups the characteristic bands were also observed.

The pyridine-2-thiolates **1** are slightly yellowish crystalline powders, which are insoluble in acetone or ether, but readily soluble in *DMF*, *DMSO*, or hot diluted *Et*OH. Compounds **1** are quite stable in the solid state, but undergo slow oxidation when being dissolved in *Et*OH or *DMSO* to form the dehydrogenated derivatives **7**. The oxidation proceeds especially easily in the case of **1c** and **1d**. Thus, ^{1}H NMR spectra of freshly prepared samples of **1c** and **1d** in *DMSO*-d_6 revealed minor signals (up to 7 molar percents according to the integral values) of by-products **7** (see Experimental for details), while IR and elemental analysis data did not give any evidence for the presence of oxidized products – at least in the solid state. It must be noted that synthesis of **1c** and **1d** has not been reported hitherto, probably due to their ready oxidation caused by prolonged reaction time or harsh conditions used before.

In conclusion, here we present a new, highly effective, and superior approach to *N*-methylmorpholinium 3,5-dicyano-4-(het)aryl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1** *via* condensation of 1-(cyanoacetyl)-3,5-dimethylpyrazole with (*E*)-2-cyano-3-(het)arylprop-2-enethioamides in the presence of *N*-methylmorpholine.

Experimental

Melting points were measured on a *Kofler* hot stage apparatus. Elemental analyses for C, H, and N were conducted using a *Perkin-Elmer* C, H, N Analyzer; their results were found to be in good agreement with the calculated values (±0.2%). IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H NMR spectra were performed on a Varian Mercury VX-200 (199.97 MHz) spectrometer on *DMSO*-d_6 solutions with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silicagel after *Pitra* with luminiscent indicator for UV 254 on the aluminum foil, binder – starch) in the acetone–heptane (1:1) system; spots were visualized with iodine vapors and UV light. The starting (*E*)-2-cyano-3-(het)arylprop-2-enethioamides **3** were prepared by condensation of corresponding aldehydes with cyanothioacetamide according to the general method reported in Ref. [18]; their physical data were found to be identical with the ones previously described [47–50]. Cyanoacetylpyrazole **8** was prepared from cyanoacetohydrazide and acetylacetone in acidic medium by known method [24–27, 32, 37].

*N-Methylmorpholinium 3,5-dicyano-4-(het)aryl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates (**1a–1d**). General Procedure (Method A)*

To the clear solution of corresponding thioamide **3a**–**3d** (3.0 mmol) and 0.5 g cyanoacetylpyrazole **8** (3.1 mmol) in 10–15 cm^3 acetone, 0.5 cm^3 *N*-methylmorpholine (4.5 mmol) were added at once. The mixture was vigorously stirred for 30 min at 25°C, the precipitated product was filtered off, washed with acetone and ether to give **1a**, **1b**, and **1d**. Due to the limited solubility of (*E*)-2-cyano-3-(3,4-dimethoxyphenyl)prop-2-enethioamide **3c** in acetone, the suspension of **3c**, **8**, and base was stirred for 24 h, then thiolate **1c** was worked up as described above.

*Tetrahydropyridine-2-thiolate (**1a**) via Three-Component Condensation of Aldehyde, Cyanothioacetamide, and Cyanoacetylpyrazole (Method B)*

To a mixture of 1.7 cm^3 *o*-chlorobenzaldehyde **6a** (15 mmol) and 1.5 g of cyanothioacetamide **5** (15 mmol) 3–4 drops *N*-methylmorpholine and 4 cm^3 acetone were added in succession. The solution was stirred with a glass stick until exothermic reaction completed and (*E*)-3-(2-chlorophenyl)-2-cyanoprop-2-enethioamide precipitated (about 5 min). To this suspension 15 cm^3 acetone, 2.6 g cyanoacetylpyrazole **8** (16 mmol) and 2.5 cm^3 *N*-methylmorpholine (22.5 mmol) were added in succession. The red solution formed quickly turns to light orange, and a white precipitate separated within 2 min. The mixture was stirred for 0.5 h, solid product was filtered off, and it was washed with hot acetone and ether to afford 4.75 g (81%) thiolate **1a**.

N-Methylmorpholinium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate, ((4R,5R)-(cis):(4R,5S)-(trans) = 9:10) (**1a**)
Yield: 96% (Method A) or 81% (Method B); m.p.: 197–200°C (dec.) (Ref. [15]: 210–212°C reported for *cis*:*trans* (1:1) mixture); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.78$ (s, NCH_3), 3.18 and 3.76 (both m, each 4H, O(CH_2CH_2)$_2$N), 4.41 (d, $^3J = 7.3$ Hz, C(4)H_{cis}), 4.45 (q, $^3J = 11.2$ Hz, C(4)H_{trans} and C(5)H_{trans}), 4.91 (d, $^3J = 7.3$ Hz, C(5)H_{cis}), 7.14–7.49 (m, 4H–*Ar*), 9.69 and 9.71 (both br s, NH_{cis}, NH_{trans}) ppm; signal of NH^+-proton was not detected, probably due to proton-deuterium exchange; IR (nujol): $\bar{\nu} = 3180$ (N–H), 2247, 2177 (2 C≡N), 1680 (C=O) cm^{-1}.

N-Methylmorpholinium 4-(4-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate, ((4S,5R)-(cis):(4S,5S)-(trans) = 1:1) (**1b**, $C_{18}H_{19}ClN_4O_2S$)
Yield: 78% (Method A); m.p.: 165–168°C (dec.); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.78$ (s, NCH_3), 3.17 and 3.75 (both m, each 4H, O(CH_2CH_2)$_2$N), 3.89 (d, $^3J = 6.3$ Hz, C(4)H_{cis}), 4.22 (dd, $^3J = 11.4$ Hz, C(4)H_{trans} and C(5)H_{trans}), 4.80 (d, $^3J = 6.3$ Hz, C(5)H_{cis}), 7.14–7.52 (m, 4H–*Ar*), 9.59 (br s, NH_{cis}, NH_{trans} overlapped) ppm; signal of NH^+-proton was not detected, probably due to proton-deuterium exchange; IR (nujol): $\bar{\nu} = 3150$ (N–H), 2253, 2185 (2 C≡N), 1700 (C=O) cm^{-1}.

N-Methylmorpholinium 3,5-dicyano-4-(3,4-dimethoxyphenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate, ((4S,5R)-(cis):(4S,5S)-(trans) = 3:4) (**1c**, $C_{20}H_{24}N_4O_4S$)
Yield: 70% (Method A); m.p.: 189–192°C (dec.); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.78$ (s, NCH_3), 3.17 and 3.72 (both m, each 4H, O(CH_2CH_2)$_2$N), 3.77 (d, $^3J = 6.7$ Hz, C(4)H_{cis}), 4.13 (dd, $^3J = 10.9$ Hz, C(4)H_{trans} and C(5)H_{trans}), 4.71 (d, $^3J = 6.7$ Hz, C(5)H_{cis}), 6.65–7.01 (m, 3H–*Ar*), 9.48 (br s, NH_{cis}, NH_{trans} overlapped) ppm; signal of NH^+-proton was not detected, probably due to proton-deuterium exchange; also a broadened peak at $\delta = 11.73$ ppm corresponding to NH proton of by-product **7** (about 6 mol%) was observed; IR (nujol): $\bar{\nu} = 3150$ (N–H), 2253, 2185 (2 C≡N), 1695 (C=O) cm^{-1}.

N-Methylmorpholinium 3,5-dicyano-4-(fur-2-yl)-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate, ((4R,5R)-(cis):(4R,5S)-(trans) = 2:1) (**1d**, $C_{16}H_{18}N_4O_3S$)
Yield: 68% (Method A); m.p.: 178–180°C (dec.); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.78$ (s, NCH_3), 3.18 and 3.76 (both m, each 4H, O(CH_2CH_2)$_2$N), 3.94 (d, $^3J = 6.5$ Hz, C(4)H_{cis}), 4.20 (dd, $^3J = 9.7$ Hz, C(4)H_{trans} and C(5)H_{trans}), 4.70 (d, $^3J = 6.5$ Hz, C(5)H_{cis}), 6.12 (m, furyl-C(3)H_{cis}), 6.24 (m, furyl-C(3)H_{trans}), 6.36 (m, furyl-C(4)H_{cis} and -C(4)H_{trans} overlapped), 7.55 (m, furyl-C(5)H_{cis}), 7.59 (m, furyl-C(5)H_{trans}), 9.45 (br s, NH_{cis}), 9.58 (br s, NH_{trans}) ppm; signal of NH^+-proton was not detected, probably due to proton-deuterium exchange; also four peaks at $\delta = 6.69$, 7.12, 7.93 (fur-2-yl), and 11.83 (NH) ppm corresponding to pyridine-2(1*H*)-thione **7** (about 7 mol%) were observed; IR (nujol): $\bar{\nu} = 3180$ (N–H), 2250, 2183 (2 C≡N), 1710 (C=O) cm^{-1}.

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