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Reactions of malonthioamides and malonamidines with methyl acetylpyruvate as a one-step method to prepare 4-thio- and 4-aminopyrrolo[3,4-*c*]pyridines

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Abstract—We report an efficient one-step approach to 4-thio and 4-aminopyrrolo[3,4-*c*]pyridines based on the selective reaction of malonthioamides and malonamidines with methyl acetylpyruvate. Structural proof is given by HMBC and HMQC spectra. A cascade heterocyclization mechanism is proposed for the reactions studied.

1. Introduction

Natural and synthetic pyridine containing compounds possess a wide spectrum of biological activities and have therefore been the subject of continuing chemical study. Pyridines fused to other heterocycles, such as thiazole, thiophene, imidazole, pyrrole, and pyrimidine attract special interest of the medicinal chemistry community because the combination from the various nuclei can increase the bioactivity or even lead to a new type of activity.[1–4] Thus compounds with high analgesic, hypotensive, and psychotropic effect were found among 6-methyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridines.[3–5] At the same time there are no data on the 4-thio- and 4-amino-substituted analogs of these compounds in the literature. Moreover, 6-methyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridines are useful intermediates in the synthesis of pyridoxine (B_6) and other derivatives of 2-methyl-3,4-pyridinedicarboxylic acid.[6–8] Therefore, the search of an efficient one-step method for the preparation of 6-methyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridines is very important.

There are a few known methods to prepare this kind of compound published in the literature. A convenient method for the synthesis of 6-methyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]-pyridine derivatives includes the cycloaddition reaction of oxazoles to maleimides followed by ring transformation of the cyclo-adduct to a pyridine ring.[7–12] 1,3-Dioxo-1*H*-pyrrolo[3,4-*c*]pyridines were prepared by reaction of formamide and aliphatic amines either with 3,4-dicarbonyl derivatives of pyridine or with 3-cyanopyridine-4-carboxylate.[6,13,14] The derivatives of 4-amino-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridine were prepared by transformation of 4-oxy-pyrazolo[3,4-*b*]-pyridines while heating at reflux temperature in ethanol for an extended time in the presence of Raney Ni.[6,15] These methods require multistep syntheses of heterocyclic precursors that limit their synthetic utility. An efficient synthesis of these compounds based on cycloaddition reaction of α-styrylcarbodiimides to the double bond of maleimides has been published by Saito et al.[16] However, this is limited to the preparation of compounds bearing aryl groups in positions 2 and 6 and arylamino and *c*-hexylamino groups at position 4 of the system. Moreover, 4-amino- and 4-thioderivatives of 1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridines that are analogous to the anticancer drug, 4-thiopurine and are therefore of special interest to medicinal chemistry, cannot be prepared by these methods.

We report in this paper a mild, one-step synthetic method leading to the 6-methyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridine system **1** based on the reaction of acetylpyruvate **3** with active methylene group compounds **2** followed by cyclization of the acetyl and carboxylate groups involving the amino groups of the malonamide to form a bicyclic system **1** (Scheme 1).

2. Results and discussions

Malonthioamides **2a**–**n** were found to react with methyl 2,4-dioxovalerate **3** in ethanol solution at room temperature in

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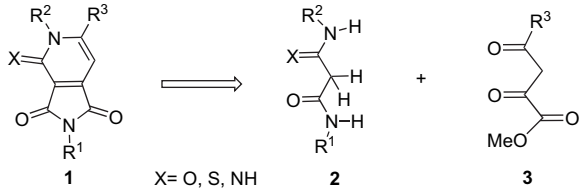


Scheme 1.

the presence of triethylamine to form novel 6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-diones **1a–n** in yields of 60–75%.

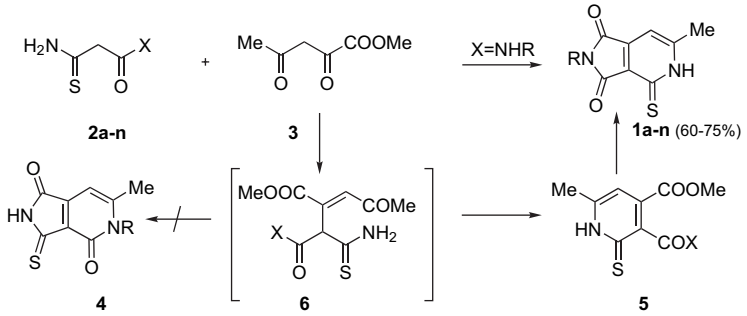
It should be noted that the malonthioamide molecules contain four nucleophilic centers and methyl 2,4-dioxovalerate bears three active carbonyl groups capable of reacting with nucleophilic reagents. Therefore, one can expect the formation of a variety of products from the reaction of compounds **2** and **3**. Because two molecules of water and one molecule of methanol were eliminated in the course of the reaction, mono- and noncyclic structures were ruled out of consideration. Structural proof for the compounds prepared is derived from their mass-spectrometry and ^{1}H and ^{13}C NMR spectra. However, the spectral data are in good accordance with both proposed structures **1** and **4**.

The ^{1}H NMR spectra of **1b** contain signals at 2.49, 2.95, and 6.99 ppm corresponding to methyl protons and the CH fragment of pyridine ring, and in addition the ^{13}C NMR spectrum includes carbon signals corresponding to the thiocarbonyl group, two carbonyl groups, and the pyridine ring at 173.2, 166.1, 165.9, 158.6, 142.8, and 124.9 ppm, respectively. The final decision in favor of the pyrrolo[3,4-*c*]pyridine-4-thione structure for compounds **1** can be made after considering the HMBC and HMQC spectra for compounds **1b** and **1c**. Thus, the HMBC spectrum for compound **1b** shows the interaction between the C-3 carbon atom and the NCH_3 protons and the correlation of C-1 with both NCH_3 and H-7 protons. The signals of C-3 at 166.1 and C-1 at 165.9 ppm in the ^{13}C NMR spectrum of compound **1b** are split into a quartet with coupling constant $^{3}J_{C(3)-NCH_3} = 3.9$ Hz and a doublet of quartets with coupling constants $^{3}J_{C(1)-NCH_3} = 4.1$ Hz and $^{3}J_{C(1)-H(7)}$=5.1 Hz. Similar correlations were observed in the HMBC and HMQC spectra of **1c**. The resonance (δ 4.69 ppm) attributed to the methylene group showed a correlation to C-1 and C-3 (δ 165.7 ppm). This confirms the presence of the pyrrole-1,3-dione moiety in **1b**,**c**. In conclusion, these data allow us to assign the structure of the compounds prepared as 4-thiopyrrolo[3,4-*c*]pyridine-1,3-diones and reject the structure of isomeric 3-thiopyrrolo[3,4-*c*]pyridine-1,4-diones **4**.

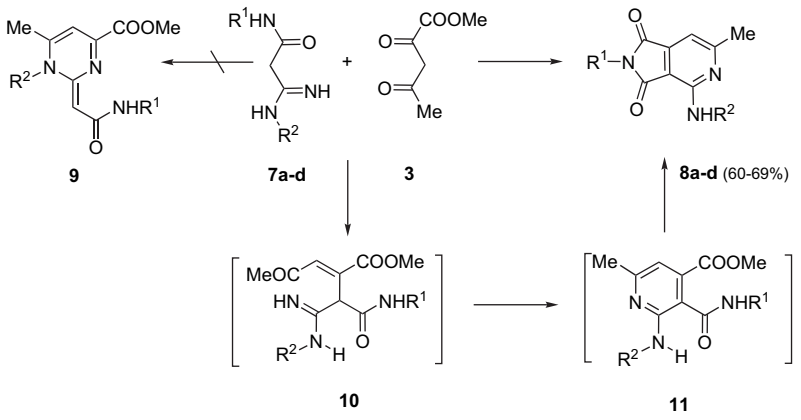
The selective product formation supports a reaction mechanism of cascade heterocyclization that includes the formation of a pyridine-2-thione **5** intermediate via attack of the active methylene group of malonthioamides **2** onto the most electrophilic $C_{(2)}$ atom of methyl 2,4-dioxovalerate **3**[17] with subsequent heterocyclization of adduct **6** due to intramolecular interaction of keto- and thioamide groups (Scheme 2). The intermolecular interaction of ester group of compound **5** onto the amide function of malonthioamide completed the reaction. This mechanism is in accordance with our experiment involving the reaction of ethyl 2-thiocarbamoylacetate with tricarbonyl compound **3** where pyridine-2(1*H*)-thione **5** (X=OEt) was obtained in good yield and with published data on the formation of 3-cyanopyridine-2(1*H*)-thiones in the reaction of 2-cyanothioacetamide with acetyl- and benzoylpyruvic esters.[1,17–20]

The malonamidine **7**, similar to malonthioamide **2** contains a number of nucleophilic centers capable of reacting with the electrophilic carbonyl groups of acetylpyruvate to form a variety of products. It is known that malonamidines react mainly as *C*,*N*-binucleophiles. Thus, their reactions with 1,3-diketones led to pyridine derivatives.[21–23] Malonamidines are also known to react as *N*,*N*′-bisnucleophiles in their reaction with either ethyl malonate or ethyl pyridylacetate to form a pyrimidine ring.[23–25] The formation of both pyridine and pyrimidine rings takes place in the reaction of malonamidines with ethyl acetate.[26]

We have found that reactions of malonamidines **7a–d** with acetylpyruvate in the conditions similar to those for the reaction of malonthioamides afford single products in moderate yield to which the 4-aminosubstituted pyrrolo[3,4-*c*]pyridine-1,3-dione structure **8** was assigned based on NMR spectra (Scheme 3). Thus ^{1}H NMR spectra of the products do not contain the signals of the methoxy group as expected in the spectra of pyrimidine **9**. Similar to 6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-diones **1a–o**, the ^{1}H NMR spectra of compounds **8** contain signals corresponding to methyl protons (2.44–2.49 ppm), and a CH fragment of the pyridine ring (6.67–6.91 ppm). The ^{13}C NMR spectrum of compound **8b** includes signals corresponding to a methyl group at 25.8, two methylene groups at 41.4 and 44.4,



Scheme 2. X=NHR, OEt; R=H (**a**), CH_3 (**b**), $CH_2C_6H_5$ (**c**), C_6H_4 (**d**), 2-$CH_3C_6H_4$ (**e**), 3-$CH_3C_6H_4$ (**f**), 4-$CH_3C_6H_4$ (**g**), 3-$MeOC_6H_4$ (**h**), 4-$MeOC_6H_4$ (**i**), 4-$EtOC_6H_4$ (**k**), 2,4-$(CH_3)_2C_6H_3$ (**l**), 3,4-$(CH_3)_2C_6H_3$ (**m**), C_6H_{11} (**n**).



Scheme 3. R^1=H, R^2=H (**a**), R^1=$CH_2C_6H_5$, R^2=$CH_2C_6H_5$ (**b**), R^1=H, R^2=$CH_2C_6H_5$ (**c**), R^1=H, R^2=CH_3 (**d**).

pyridine moiety at 102.9, 105.8, 142.0, 153.6, and 167.0 and two carbonyls at 167.7 and 169.6 ppm.

The methylene proton signal of the 4-benzylamino group in the spectra of **8b** at 4.71 ppm is a doublet and the signal of NH at 6.59 ppm is a triplet. The signal of 4-methylamino group in the spectrum of **8d** also shows as a doublet. These data are in agreement with the structure **8** having an exocyclic aminosubstituted function.

The final decision in favor of the 4-aminopyrrolo[3,4-*c*]pyridine structure for compounds **8** can be made after considering the HMQC and HMBC spectra for compound **8b**. Thus, the HMBC spectrum for compound **8b** shows the interaction between the carbon atom C-3 and the protons of the NCH_2 group and the correlation of C-1 with both protons of NCH_2 and H-7. The signals of C-1 at 167.7 ppm in the ^{13}C NMR spectrum of compound **8b** are split into a doublet (^3J=3.5 Hz). The signal of N–CH_2 group at 4.7 ppm shows a correlation with C-1 (167.7 ppm) and C-3 (169.6 ppm). Similar correlations were observed in the HMBC and HMQC spectra of **8a**.

We can conclude that malonamidines, independent of the substituents on the amide and amidine groups, similar to malonthioamides **2**, react with acetylpyruvate as *C*,*N*,*N*-trinucleophiles. The interaction of the 2-keto group of acetylpyruvate **3** with the active methylene group of malonamidines **7** first forms adduct **10**. Then, the unsubstituted amino group of the amidine function rather than the substituted one takes part in the formation of the pyridine ring of intermediate **11**. The final product **8** results from the intramolecular condensation of the ester group onto the amide function of pyridine **11**.

3. Conclusions

Reaction of malonthioamides and malonamidines with acetylpyruvate by analogy to heterocyclization reactions of malonamide[6] represents an efficient, one-step approach to pyrrolo[3,4-*c*]pyridines with carbonyl, thiocarbonyl, and amino functions at position 4. The products are easily isolated by simple filtration and are pure enough for further modifications. The method is particularly useful for the synthesis of large amounts of various derivatives of pyrrolo[3,4-*c*]pyridines for biological evaluations.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AMX400 with $SiMe_4$ as internal reference in DMSO-d_6+CCl_4 solution. Mass spectra were obtained on a Varian MAT311A instrument using the electron impact ionization technique (40–200 °C, 70 eV). Reactions were monitored by TLC (Silyfol® on aluminum foil plates) in $CHCl_3$–EtOH (9:1), $CHCl_3$–EtOH–NH_4OH (15:8:1), acetone–hexane (3:5) visualized under UV light. The melting points are uncorrected.

The malonthioamides **2a**–**n** were prepared by reaction of the corresponding nitriles with hydrogen sulfide, as reported.[27] Carboxamidoacetamidine hydrochloride **7a** was prepared by the procedure reported,[28] amidines **7b–d** have been synthesized according to the literature.[29,30]

4.2. Synthesis of 6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-diones (1a–n)

General procedure. Methyl 2,4-dioxovalerate **3** (1.0 mmol) and triethylamine (1.0 mmol) were added to a suspension of malonthioamides **2a**–**n** (1.0 mmol) in ethanol (5 mL). The reaction mixture was allowed to stir at room temperature for 2 h. After acidification with 5% acetic acid to pH 4–5 the reaction mixture was left at room temperature for 3 h. The red precipitate was filtered off, washed with H_2O, hot ethanol, and hexane.

4.2.1. 6-Methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1a). The title compound was obtained as a red solid in 69% yield (0.26 g) from malonthioamides **2a** (0.22 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 264–267 °C; ^1H NMR: δ=2.49 (s, 3H, CH_3), 6.81 (s, 1H, =CH), 11.15 (s, 1H, NH), 13.90 (s, 1H, NH); MS, *m*/*z* (%): 194 (100) $M^{+\bullet}$. Anal. Found: C, 49.08; H, 2.92; N, 14.84. Calcd for $C_8H_6N_2O_2S$: C, 49.49; H, 3.12; N, 14.42.

4.2.2. 2,6-Dimethyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1b). The title compound was obtained as a red solid in 72% yield (0.30 g) from malonthioamides **2b** (0.25 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 250–253 °C; ^{1}H NMR: δ=2.49 (s, 3H, CH_3), 2.95 (s, 2H, NCH_3), 6.99 (s, 1H, =CH), 14.0 (s, 1H, NH); ^{13}C NMR: δ=19.6 (CH_3), 23.8 (NCH_3), 105.3 (d×q, C-7, J=5.1 Hz), 124.9 (d, C-3′), 142.8 (s, C-7′), 158.6 (m, C-6), 165.9 (q, C-1, J=4.2 Hz), 166.1 (q, C-3, ^3J=3.9 Hz), 173.2 (s, C-4); MS, *m/z* (%): 208 (100) $M^{+\bullet}$. Anal. Found: C, 52.18; H, 3.64; N, 13.74. Calcd for $C_9H_8N_2O_2S$: C, 51.90; H, 3.90; N, 13.45.

4.2.3. 2-Benzyl-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1c). The title compound was obtained as a red solid in 64% yield (0.36 g) from malonthioamides **2c** (0.42 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 273–275 °C; ^{1}H NMR: δ=2.48 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.01 (s, 1H, =CH), 7.2–7.4 (m, 6H, Ph), 14.04 (s, 1H, NH); ^{13}C NMR: δ=19.6 (CH_3), 40.9 (s, CH_2), 105.5 (d×q, C-7, J=5.7 Hz), 124.6 (d, C-3′), 127.3, 128.4, 136.4 (Ph), 142.7 (s, C-7′), 158.9 (m, C-6), 165.7 (q, C-1, J=4.1 Hz), 166.1 (q, C-3, ^3J=3.9 Hz), 173.2 (s, C-4); MS, *m/z* (%): 284 (100) $M^{+\bullet}$. Anal. Found: C, 63.79; H, 4.05; N, 9.56. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.33; H, 4.25; N, 9.86.

4.2.4. 6-Methyl-2-phenyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1d). The title compound was obtained as a red solid in 68% yield (0.28 g) from malonthioamides **2d** (0.40 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 247–251 °C; ^{1}H NMR: δ=2.54 (s, 3H, CH_3), 6.96 (s, 1H, =CH), 7.30–7.52 (m, 5H, C_6H_5), 14.03 (s, 1H, NH); MS, *m/z* (%): 270 (100) $M^{+\bullet}$. Anal. Found: C, 61.87; H, 3.88; N, 10.89. $C_{14}H_{10}N_2O_2S$. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.22; H. 3.73; N, 10.36.

4.2.5. 2-(2-Methylphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1e). The title compound was obtained as a red solid in 61% yield (0.34 g) from malonthioamides **2e** (0.42 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 258–261 °C; ^{1}H NMR: δ=2.14 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.99 (s, 1H, =CH), 7.10–7.40 (m, 4H, Ar), 14.10 (s, 1H, NH); MS, *m/z* (%): 284 (100) $M^{+\bullet}$. Anal. Found: C, 63.69; H, 4.12; N, 10.01. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.33; H, 4.25; N, 9.85.

4.2.6. 2-(3-Methylphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1f). The title compound was obtained as a red solid in 73% yield (0.42 g) from malonthioamides **2f** (0.42 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 230–235 °C; ^{1}H NMR: δ=2.14 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.98 (s, 1H, =CH), 7.10–7.25 (m, 3H, Ar), 7.3–7.40 (m, 1H, Ar), 14.10 (s, 1H, NH); MS, *m/z* (%): 284 (100) $M^{+\bullet}$. Found, %: C, 63.69; H, 4.07; N, 10.09. $C_{15}H_{12}N_2O_2S$. Calcd, %: C, 63.33; H, 4.25; N, 9.85.

4.2.7. 2-(4-Methylphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1g). The title compound was obtained as a red solid in 68% yield (0.38 g) from malonthioamides **2g** (0.42 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 295–297 °C; ^{1}H NMR: δ=2.40 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.95 (s, 1H, =CH), 7.0–7.20 (m, 4H, Ar), 14.10 (s, 1H, NH); MS, *m/z* (%): 284 (100) $M^{+\bullet}$. Found, %: C, 63.75; H, 4.33; N, 9.41. $C_{15}H_{12}N_2O_2S$. Calcd, %: C, 63.33; H, 4.25; N, 9.85.

4.2.8. 2-(3-Methoxyphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1h). The title compound was obtained as a red solid in 68% yield (0.42 g) from malonthioamides **2h** (0.45 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 262–264 °C; ^{1}H NMR: δ=2.54 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.90–7.30 (m, 3H, Ar), 6.98 (s, 1H, =CH), 7.38 (t, 1H, Ar), 14.08 (s, 1H, NH); MS, *m/z* (%): 300 (100) $M^{+\bullet}$. Anal. Found: C, 59.61; H, 4.2; N, 9.47. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.32.

4.2.9. 2-(4-Methoxyphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1i). The title compound was obtained as a red solid in 73% yield (0.44 g) from malonthioamides **2i** (0.45 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 252–255 °C; ^{1}H NMR: δ=2.52 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.04 and 7.30 (d, 4H, AB, Ar, J=2.1 Hz), 7.06 (s, 1H, =CH), 14.08 (s, 1H, NH); MS, *m/z* (%): 300 (100) $M^{+\bullet}$. Anal. Found: C, 60.26; H, 4.17; N, 9.12. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.32.

4.2.10. 2-(4-Ethoxyphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1k). The title compound was obtained as a red solid in 72% yield (0.45 g) from malonthioamides **2k** (0.47 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol). Mp 252–255 °C; ^{1}H NMR: δ=1.39 (t, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 6.90–7.0 (m, 2H, Ar), 6.99 (s, 1H, =CH), 7.20–7.36 (m, 2H, Ar), 13.90 (s, 1H, NH); MS, *m/z* (%): 314 (100) $M^{+\bullet}$. Anal. Found: C, 61.52; H, 4.24; N, 8.89. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.15; H, 4.49; N, 8.91.

4.2.11. 2-(2,4-Dimethylphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1l). The title compound was obtained as a red solid in 72% yield (0.43 g) from malonthioamides **2l** (0.44 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 277–279 °C; ^{1}H NMR: δ=2.08 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.98 (s, 1H, =CH), 7.05–7.12 (m, 2H, Ar), 7.16 (s, 1H, Ar), 14.10 (s, 1H, NH); MS, *m/z* (%): 298 (100) $M^{+\bullet}$. Anal. Found: C, 64.73; H, 4.56; N, 9.24. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.43; H, 4.73; N, 9.40.

4.2.12. 2-(3,4-Dimethylphenyl)-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1m). The title compound was obtained as a red solid in 69% yield (0.41 g) from malonthioamides **2m** (0.44 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 285–287 °C, yield 69%;

^{1}H NMR: δ=2.30 (s, 6H, 2CH_3), 2.53 (s, 3H, CH_3), 6.94 (s, 1H, =CH), 7.0–7.10 (m, 2H, Ar), 7.20–7.25 (s, 1H, Ar), 14.10 (s, 1H, NH); MS, *m/z* (%): 298 (100) $M^{+\bullet}$. Anal. Found: C, 64.34; H, 4.53; N, 9.68. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.43; H, 4.73; N, 9.40.

4.2.13. 2-Cyclohexyl-6-methyl-4-thioxo-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-dione (1n). The title compound was obtained as a red solid in 68% yield (0.38 g) from malonthioamides **2n** (0.40 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 277–283 °C; ^{1}H NMR: δ=1.1–1.43 (m, 2H, CH_2), 1.66–1.68 (m, 2H, CH_2), 1.8–1.9 (m, 2H, CH_2), 1.97–2.15 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 3.8–3.95 (m, 1H, CH), 6.88 (s, 1H, =CH). MS, *m/z* (%): 276 (100) $M^{+\bullet}$. Anal. Found: C, 61.17; H, 5.41; N, 10.56. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.82; N, 10.13.

4.2.14. 1-(4-Acetyl-6-methyl-2-thioxo-1,2-dihydropyridin-3-yl)-ethanone (5). The compound **5** was obtained by analogy with **1a** as yellow crystals in 81% yield (0.36 g) from ethyl 2-thiocarbamoylacetate (0.29 g, 2.0 mmol), methyl 2,4-dioxovalerate **3** (0.28 g, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol). Mp 120–123 °C; ^{1}H NMR: δ=1.26 (t, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.24 (q, 2H, CH_2), 6.91 (s, 1H, =CH), 14.1 (s, 1H, NH); MS, *m/z* (%): 225 (51.3) $M^{+\bullet}$. Anal. Found: C, 58.99; H, 6.07; N, 5.81. Calcd for $C_{11}H_{13}NO_4S$: C, 58.63; H, 5.81; N, 6.20.

4.3. Synthesis of 6-methyl-4-amino-4,5-dihydropyrrolo[3,4-*c*]pyridine-1,3-diones (8a–d)

4.3.1. 4-Amino-6-methylpyrrolo[3,4-*c*]pyridine-1,3-dione (8a). Methyl 2,4-dioxovalerate **3** (0.53 g, 3.6 mmol) and triethylamine (0.5 mL, 3.6 mmol) were added to a suspension of malonamidoamidine hydrochloride **7a** (0.50 g, 3.6 mmol) in ethanol (5 mL). The reaction mixture was allowed to stir at room temperature for 3 h. The yellow precipitate of compound **8a** was filtered off, washed with ethanol and hexane, yield 0.48 g (69%). Mp 264–268 °C; ^{1}H NMR: δ=2.46 (s, 3H, CH_3), 6.61 (s, 2H, NH_2), 6.68 (s, 1H, =CH), 10.89 (s, 1H, NH); ^{13}C NMR: δ=24.8 (CH_3), 102.8 (d, C-3′), 105.2 (d×q, C-7, *J*=6.2 Hz), 142.9 (s, C-7′), 154.3 (br s, C-4), 166.0 (m, C-6), 168.7 (d, C-1, *J*=4.6 Hz), 170.49 (s, C-3,); MS, *m/z* (%): 177 (100) $M^{+\bullet}$. Anal. Found: C, 54.42; H, 4.25; N, 23.90. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.70.

4.3.2. 2-Benzyl-4-benzylamino-6-methylpyrrolo[3,4-*c*]pyridine-1,3-dione (8b). The title compound was obtained by analogy with **8a** as yellow solid in 62% yield (0.22 g) from malonamidine hydrochloride **7b** (0.32 g, 1.0 mmol), methyl 2,4-dioxovalerate **3** (0.15 g, 1.0 mmol), and triethylamine (0.15 mL, 1.0 mmol). Mp 250–252 °C; ^{1}H NMR: δ=2.46 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 4.72 (d, 2H, CH_2), 6.59 (t, 1H, NH), 6.80 (s, 1H, =CH), 7.20–7.35 (m, 10H, Ar); ^{13}C NMR: δ=19.6 (CH_3), 40.9 (s, CH_2), 105.5 (d×q, C-7, *J*=5.7 Hz), 124.6 (d, C-3′), 127.3, 128.4, 136.4 (Ph), 142.7 (s, C-7′), 158.9 (m, C-6), 165.7 (q, C-1, *J*=4.1 Hz), 166.1 (q, C-3, ^3J=3.9 Hz), 173.2 (s, C-4); MS, *m/z* (%): 357 (100) $M^{+\bullet}$. Anal. Found: C, 74.02; H, 5.16; N, 11.95. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.77.

4.3.3. 4-Benzylamino-6-methylpyrrolo[3,4-*c*]pyridine-1,3-dione (8c). Methyl 2,4-dioxovalerate **3** (0.13 g, 0.89 mmol) and triethylamine (0.11 mL, 0.72 mmol) were added to a suspension of malonamidoamidine hydrochloride **7c** (0.20 g, 0.72 mmol) in ethanol (5 mL). The reaction mixture was allowed to stir at room temperature for 3 h. The solid was filtered off. Evaporation of the filtrate gave yellow crystals, yield 0.14 g (60%). Mp 264–268 °C (from ethanol); ^{1}H NMR: δ=2.44 (s, 3H, CH_3), 4.69 (d, 2H, CH_2), 6.67 (s, 1H, =CH), 7.20–7.37 (m, 6H), 11.12 (s, 1H, NH); MS, *m/z* (%): 267 (100) $M^{+\bullet}$. Anal. Found: C, 67.18; H, 4.78; N, 16.02. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.71.

4.3.4. 6-Methyl-4-methylaminopyrrolo[3,4-*c*]pyridine-1,3-dione (8d). Methyl 2,4-dioxovalerate **3** (0.38 g, 2.6 mmol) and triethylamine (0.96 mL, 2.6 mmol) were added to a suspension of malonamidoamidine hydrochloride **7d** (0.40 g, 2.6 mmol) in ethanol (5 mL). The reaction mixture was allowed to stir at room temperature for 3 h. The solid was filtered off. The filtrate was concentrated in vacuum, and the residue chromatographed on a column, which was eluted with chloroform. Evaporation of the eluent gave yellow crystals, yield 0.3 g (60%). Mp 273–275 °C; ^{1}H NMR: δ=2.48 (s, 3H, CH_3), 3.01 (d, 3H, NCH_3), 6.67 (s, 1H, =CH), 6.59 (d, 1H, NH), 10.86 (s, 1H, NH); MS, *m/z* (%): 191 (100) $M^{+\bullet}$. Anal. Found: C, 56.75; H, 4.65; N, 21.62. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.76; N, 21.99.

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