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Cascade Reactions

Unexpected Synthesis of 2,3,5,6-Tetrahydro-1*H*-pyrrolo[3,4-*c*]-pyridine-1,3,6-triones by a Double Michael Addition/CS_2 Extrusion/Double Cyclization Sequence

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Abstract: Bis adducts derived from a double Michael addition of rhodanine to an azo-ene system of two molecules of 1,2-diaza-1,3-dienes (DDs) have furnished the corresponding 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones by means of a CS_2 extrusion/double cyclization sequence. The incorporation of two units (4 and 2 atoms) of DDs into the fused bicyclic heterocycles represents a new application of this versatile class of molecules in heterocyclic synthesis.

Introduction

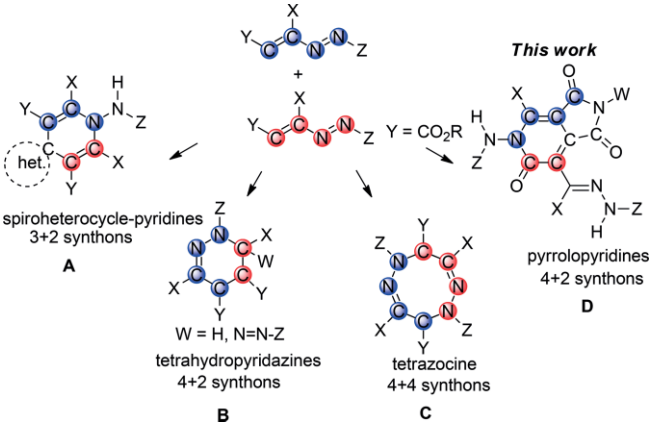
One of the most intriguing targets of organic chemists is the possibility to obtain complex transformations in a single-step reaction by starting from a set of various reagents to give directly the final product.

This kind of transformations, in which several bonds are formed in one sequence under the same reaction conditions without isolating the intermediates and without adding additional reagents or catalysts, are commonly called domino or cascade reactions.[1,2]

It appears clear that the advantages of this synthetic methodology can be of economical, ecological, and of operative interest, because it increases the synthetic efficiency and decreases the amount of solvents, reagents, and catalysts used and the number of laboratory operations required.[1,2]

The utility and versatility of 1,2-diaza-1,3-dienes (DDs) in the construction of a variety of heterocyclic rings are well known and are demonstrated by significant activity in this field over recent years.[3] In particular, they can react as Michael acceptors in conjugated additions, and they can also be employed in cycloaddition reactions with a wide range of partners.[3,4]

In most cases reported in the literature for the Michael addition, DD participates with one unit in the construction of the final heterocycle, whereas there are only a few examples in which it takes part with two units. In particular, in the spiroheterocycle-pyridines previously synthesized by our group starting from DDs and some oxindole or barbiturate derivatives, the two molecules of DDs contribute to the final pyridine core with 3 and 2 atoms (Scheme 1; structure **A**).[5,6] Another example is represented by pyridazines derived from the cyclodimerization of two molecules of DDs that results in a formal [4+2] cycloaddition (Scheme 1; structure **B**).[7]



Scheme 1. Participation of two DD units in a heterocyclic assembly.

Recently, Shelke and Suryavanshi have reported the synthesis of a tetrazocine derived by a [4+4] cycloaddition reaction (Scheme 1; structure **C**).[7a]

In the present work, for the first time, two units of DDs participate in the construction of a system that contains two fused heterocycles of the formed pyrrolo-pyridines with 4 and 2 atoms (Scheme 1; structure **D**). In particular, one unit of the DDs contributes in both the pyridine and pyrrole nuclei of the final molecule.

Our initial intent was to obtain 4-oxo-2-thioxo-1-thia-3,8-diazaspiro[4.5]deca-6,9-diene-6,10-dicarboxylates **A** (Figure 1, Route B), because rhodanines represent a privileged scaffold in drug discovery, and they are known to exhibit a wide spectrum of pharmacological properties.[8]

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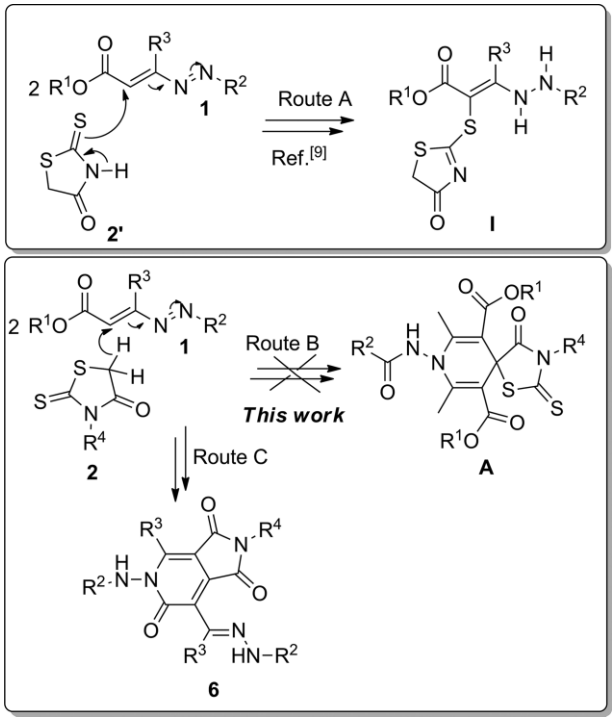


Figure 1. Intent to synthesize 4-oxo-2-thioxo-1-thia-3,8-diazaspiro[4.5]deca-6,9-diene-6,10-dicarboxylates **A** by supposed Route B and obtained Route C.

Previously, some of us investigated the reaction between DDs **1** and *N*-unsubstituted rhodanines **2′** (Figure 1, Route A).[9] In this case, the sulfur atom of the rhodanines acted as a nucleophile. To avoid this eventuality, we planned to explore the reaction between 2 equiv. of DDs **1** and some *N*-substituted rhodanine derivatives **2** in which the carbon atom at position 5 could act as nucleophile.

After the formation of bis adducts by means of a double Michael addition of one molecule of rhodanine **2** to two molecules of DD **1**, the intramolecular ring closure could have furnished the desired spiro derivatives **A** in analogy to what was previously observed[5,6] (Figure 1, Route B).

But the reactions surprisingly furnished the interesting 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6** (Figure 1, Route C). These bicyclic compounds represent a new family of HIV-1 integrase inhibitors that showed low micromolar inhibitory potency in vitro HIV-1 integrase assays, with good selectivity for strand-transfer reactions relative to 3′-processing inhibition.[10] They have reported in the literature to be prepared by "Plummer cyclization-deprotonation-cycloaddition" cascade reactions of imidosulfoxides.[10]

Results and Discussion

Several methods are reported in the literature for the synthesis of rhodanines.[11] To start our investigations, we have prepared 3-ethyl-, 3-phenyl-, 3-(4-chlorophenyl)- and 3-(4-methoxy)-2-thioxothiazolidin-4-ones **2a**–**2d** in accordance with the procedure reported by Ravi et al.[11a]

So, we began our studies by carrying out a preliminary reaction between 2 equiv. of DD **1d** and 3-phenylrhodanine **2b**, chosen as examples, under basic conditions, by using 2 equiv. of K_2CO_3. As expected, bis(hydrazone)-functionalized rhodanine **4d** was formed in 93 % yield, which resulted from a double Michael-type addition of rhodanine **2b** to 2 equiv. of DD **1d** (Table 1).

At this point, we have dealt with the development of a procedure for the cyclization of **4d** by testing several solvents, such as CH_2Cl_2, tetrahydrofuran (THF), EtOH, and acetonitrile, at different temperatures (room temp., reflux). Furthermore, a series of catalysts were used, such as K_2CO_3, NaH, NaH/Amberlyst 15H, MeONa, trifluoroacetic acid (TFA), $CuCl_2$, and $ZnCl_2$, and different molar ratios of **4d**/catalyst were employed (Table 1). We observed that with EtOH or CH_3CN and NaH in an equimolar ratio (Table 1, Entries 8 and 9) the reactions gave complicated mixtures. The same behavior was pointed out by the reaction in CH_2Cl_2 with TFA as catalyst (Table 1, Entry 1), whereas no reactions were detected with the use of $CuCl_2$ or $ZnCl_2$ in catalytic amounts (Table 1, Entries 13 and 14). In all the other cases (Table 1, Entries 2–7 and 10–12), instead of the expected 4-oxo-2-thioxo-1-thia-3,8-diazaspiro[4.5]deca-6,9-diene-6,10-dicarboxylate, a different product was achieved, which was isolated and characterized as 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione **6e**, the formation of which took place with the loss of CS_2. By taking into consideration that its boiling point is 46.3 °C, we decided to perform other tests at 55 °C and keep open the reaction flask to facilitate the removal of CS_2 and use the best conditions found at room temperature, such as THF and base (Table 1, Entries 15–17). The best results in terms of highest yield of **6e** (61 %) involve the use of 5 equiv. of K_2CO_3 (Table 1, Entry 17).

At this point, we tested the same reaction between **1d** and **2b** with K_2CO_3 (5 equiv.) at 55 °C to obtain 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione **6e** directly in a one-pot procedure. Indeed, product **6e** was formed in 66 % yield (Table 1, Entry 18).

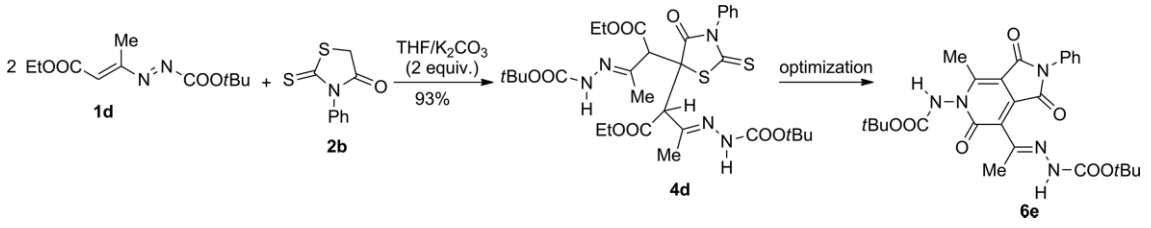
So, with these optimal conditions in hand, we explored the reactions of various DDs **1a**–**1h** with rhodanines **2a**–**2d** both by step-by-step (Scheme 2, Path A) and one-pot methods (Scheme 2, Path B).

In particular, by applying Path A, the reaction of DDs **1a**, **1c**–**1e** with rhodanines **2a**–**2d** in THF with K_2CO_3 (2 equiv.) at room temperature, bis(hydrazone)-functionalized rhodanines **4a**–**4f** were obtained in good to excellent yields (79–93 %), and the reactions were completed in 0.1–0.5 h (Scheme 2, Path A; Table 2).

Basic treatment of **4a**–**4f** with K_2CO_3 (5 equiv.) in THF at 55 °C in an open flask furnished the corresponding 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6a**, **6c**–**6e**, **6j**, and **6l**, in 2.0–5.0 h in acceptable yields (39–61 %; Scheme 2, Path A; Table 2).

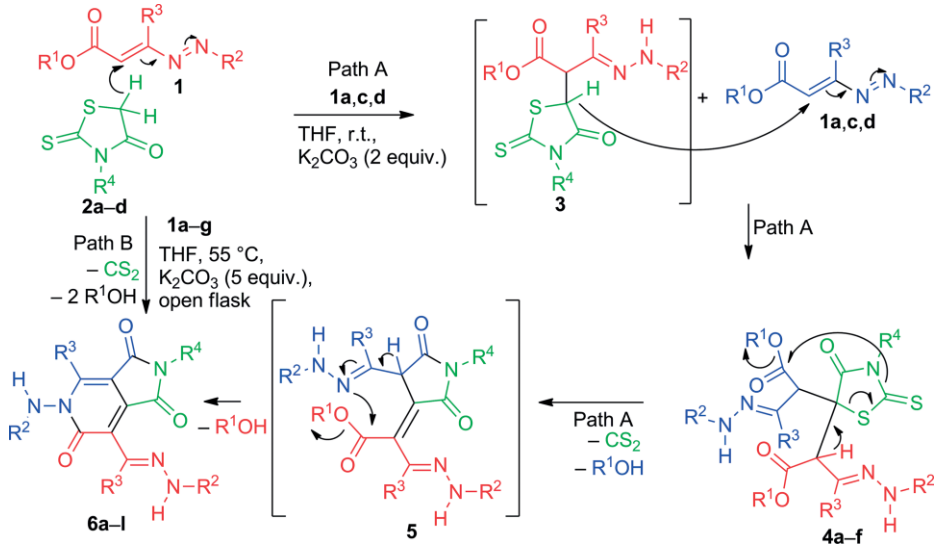
More conveniently, 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]-pyridine-1,3,6-triones **6a**–**6l** were obtained in good yields (43–66 %) by means of a one-pot procedure by carrying out the reaction between DDs **1a**–**1g** and rhodanines **2a**–**2d** in THF with K_2CO_3 (5 equiv.) at 55 °C in an open flask. Under these

Table 1. Screening of different conditions in the cyclization reaction of bis(hydrazone)-functionalized rhodanine **4d** for the synthesis of 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione **6e**.[a]



Entry	Solvent	Temperature [°C]	Catalyst (C)	Molar ratio of **4d**/C	Yield of **6e**[b] [%]
1	CH_2Cl_2	room temp.	TFA	1:0.1	complicated mixture
2	THF	room temp.	NaH	1:0.1	14
3	THF[c]	room temp.	NaH	1:1.5	14
4	THF	room temp.	NaH	1:2	16
5	THF	room temp.	NaH	1:3	13
6	THF	room temp.	NaH, then Amberlyst 15H	1:2:2	25
7	THF	reflux	NaH, then Amberlyst 15H	1:0.75:0.75	15
8	EtOH	room temp.	NaH	1:1	complicated mixture
9	CH_3CN	room temp.	NaH	1:1	complicated mixture
10	THF	room temp.	NaOMe	1:0.1	8
11	THF	room temp.	NaOMe	1:1.5	32
12[c]	THF	room temp.	NaOMe	1:5	21
13	CH_2Cl_2	room temp.	$CuCl_2$	1:0.1	no reaction
14	CH_2Cl_2	room temp.	$ZnCl_2$	1:0.1	no reaction
15	THF	55 °C	NaH	1:1	21
16	THF	55 °C	NaOMe	1:1	52
17	***THF***	***55 °C***	***K_2CO_3***	***1:5***	***61***
18[d]	***THF***	***55 °C***	***K_2CO_3***	***1:5***[e]	***66***[f]

[a] The reactions were performed on a 0.5 mmol scale of **4d** in 3 mL of solvent. [b] Yields of isolated **6e** based on **4d**. [c] The reaction was performed on a 0.5 mmol scale of **4d** in 100 mL of solvent. [d] The reaction was performed in a one-pot procedure by starting from **1d** (1.0 mmol) and **2b** (0.5 mmol). [e] Molar ratio of rhodanine **2b**/K_2CO_3. [f] Yield of isolated **6e** based on **2b**.



Scheme 2. Synthesis of dialkyl 2,2′-[(3-substituted 4-oxo-2-thioxothiazolidine-5,5-diyl)bis(4-alkoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylates) **4a**–**4f** and of 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6a**–**6l**; proposed mechanism.

conditions the reactions were completed in 1.0–5.0 h (Scheme 2, Path B; Table 2).

Any attempt to isolate mono adduct **3**, which derives from the Michael-type addition of rhodanine **2** to 1 equiv. of DD **1**, failed (Scheme 1); in fact, from tests carried out under different conditions with a DD/rhodanine equimolar ratio, only bis adducts **4** were formed. If products **3** have been obtained, it would have given us the opportunity to add them to DD molecules different from the starting ones.

The plausible mechanism of this cascade reaction involves preliminary double attack (Michael-type) of the carbon atom in the 5 position of rhodanine **2** to the terminal carbon atom of

Table 2. Yields and reaction times for the synthesis of dialkyl 2,2′-[(3-substituted-4-oxo-2-thioxothiazolidine-5,5-diyl)bis(4-alkoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylates) **4a**–**4f** and of 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6a**–**6l**.

Entry	**1**	R^1	R^2	R^3	**2**	R^4	**4**	Time [h]	Yield [%][a]	**6**	Time [h]	Yield [%][b]	Time [h]	Yield [%][c]
1	**1a**	Et	CO_2Me	Me	**2a**	Et	**4a**	0.1	79	**6a**	4.5	42	4.0	44
3	**1b**	Me	CO_2tBu	Me	**2a**	Et				**6b**			5.0	58
4	**1a**	Et	CO_2Me	Me	**2b**	Ph	**4b**	0.1	85	**6c**	5.0	53	4.5	60
5	**1c**	Me	CO_2Et	Me	**2b**	Ph	**4c**	0.2	92	**6d**	5.0	53	4.0	55
6	**1d**	Et	CO_2tBu	Me	**2b**	Ph	**4d**	0.2	93	**6e**	4.5	61	4.0	66
7	**1e**	Me	CO_2Et	Bu	**2b**	Ph				**6f**			5.0	63
8	**1f**	Et	CO_2Bn	Me	**2b**	Ph				**6g**			4.5	43
9	**1g**	Me	CO_2Me	Me	**2c**	4-ClC_6H_4				**6h**			4.0	46
10	**1b**	Me	CO_2tBu	Me	**2c**	4-ClC_6H_4				**6i**			4.0	51
11	**1c**	Me	CO_2Et	Me	**2c**	4-ClC_6H_4	**4e**	0.2	88	**6j**	5.0	39	4.5	58
12	**1c**	Me	CO_2Et	Me	**2d**	4-$MeOC_6H_4$				**6k**			1.5	59
13	**1d**	Et	CO_2tBu	Me	**2d**	4-$MeOC_6H_4$	**4f**	0.5	93	**6l**	2.0	61	1.0	64

[a] Yields of pure isolated products referred to rhodanines **2a**–**2d**. [b] Yields of pure isolated products referred to bis(hydrazones) **4a**–**4f** (Scheme 2, Path A). [c] Yields of pure isolated products referred to rhodanines **2a**–**2d** in the one-pot procedure (Scheme 2, Path B).

the azo-ene system of two molecules of DD **1**, with the formation of bis(hydrazone) intermediate **4**. The key step in the construction of the tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione system is the opening of the 2-thioxothiazolidin-4-one ring, which results in the loss of CS_2. This process is triggered by the removal from the base of the acidic proton originally located in the 4-position of the first azo-ene molecule, with subsequent activation of the nitrogen atom from the rhodanine core. Its nucleophilic attack on the ester function of the second DD molecule promotes the formation of the pyrrolidine-2,5-dione core of non-isolated intermediate **5**. Further cyclization to obtain the pyridin-2(1*H*)-one nucleus occurs as a result of the basic removal of the analogous proton that derives from the second molecule of DD that promotes the nucleophilic attack of the sp^2 nitrogen atom at the ester carbonyl function originally located in the first DD (Scheme 2).

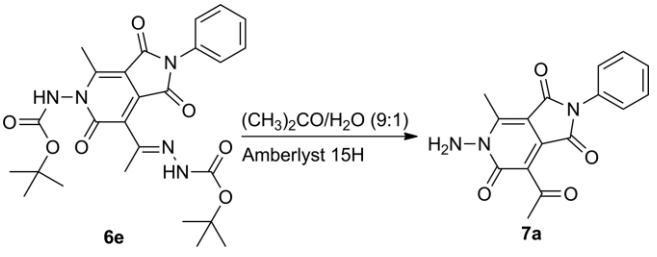
It is noteworthy that a double interaction between the two fragments derived from the two DDs occurs, and in the one-pot procedure this cascade reaction furnishes two new single carbon–nitrogen bonds and a single and a double carbon–carbon bond.

The two activated protons play a crucial role by promoting the double nitrogen nucleophilic attack onto the ester function of the other fragments.

To the best of our knowledge, just one example of ring-opening/ring-closing process of the rhodanine core is reported in the literature.[12] Differently from this, our sequence occurs with the loss of a molecule of carbon disulfide, which activates the substituted nitrogen atom of the rhodanine as nucleophile in the first cyclization event.

The structures of compounds **4** and **6** were confirmed by 1D and 2D NMR spectroscopic measurements, and the data are directly comparable to those reported in the literature for similar compounds.[10,13]

Further evidence of the proposed structure for compounds **6** was furnished by the hydrolytic cleavage of the hydrazone moiety in position 7 of the pyridine ring of compound **6e**, chosen as an example, that was obtained under heterogeneous conditions with acetone/water (9:1) and Amberlyst 15H.[14] Under these acidic conditions also the loss of the *tert*-butoxycarbonyl moiety occurred to give the corresponding 7-acetyl-5-amino-4-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-(2*H*,5*H*)-trione **7a** in very good yield (83 %; Scheme 3).[14]



Scheme 3. Hydrolytic cleavage of 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]-pyridine-1,3,6-trione **6e** to 7-acetyl-5-amino-4-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione **7a**.

Conclusions

By starting from 1,2-diaza-1,3-dienes and rhodanine derivatives, we have developed a synthetic strategy to have access to 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones by means of a double Michael addition/CS_2 extrusion/double cyclization sequence. To the best of our knowledge, this work represents the first example of a ring-opening/ring-closing process with concomitant extrusion of carbon disulfide from the rhodanine core. The easy availability of the starting materials, the simplicity of the experimental method, and the potential biological activities and utilities of products can increase the synthetic usefulness of this new procedure. Furthermore, by employing a step-by-step approach highly functionalized rhodanines could be easily obtained in satisfactory yields.

Experimental Section

General Information: All chemicals and solvents were purchased from commercial suppliers and used as received. Rhodanines **2a**–**2d** were obtained in accordance with the procedure reported in the literature:[11a] A mixture of thioglycolic acid (0.92 g, 10 mmol) and ethyl, phenyl, 4-chlorophenyl, or 4-methoxyphenyl isothio-

cyanates (12 mmol) in methanol (8 mL) and water (100 mL) was heated in an oil bath at 100 °C for 4 h. 1,2-Diaza-1,3-dienes **1a**–**1g** were prepared as reported[15] and used as (*E*,*E*)/(*E*,*Z*) isomers. Melting points were determined in open capillary tubes. FTIR spectra were obtained as nujol mulls. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals by using values of δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon (middle peak) in [D$_6$]DMSO, and δ = 7.27 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. All NH groups exchanged with D_2O. Pre-coated aluminum oxide plates (0.25 mm) were employed for analytical thin layer chromatography. All new compounds showed satisfactory elemental analysis. Mass spectra were recorded in the ESI mode. The nomenclature was generated by using ACD/IUPAC Name (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON, Canada.

General Procedure for the Synthesis of Dialkyl 2,2′-[(3-Substituted 4-oxo-2-thioxothiazolidine-5,5-diyl)bis(4-alkoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylates) 4a–4f: To a magnetically stirred solution of 1,2-diaza-1,3-dienes **1a**, **1c**, or **1d** (4.2 mmol) and 3-ethyl-, 3-phenyl-, 3-(4-chlorophenyl)-, or 3-(4-methoxyphenyl)-2-thioxothiazolidin-4-ones **2a**–**2d** (2.0 mmol) in THF (10 mL) at room temperature, potassium carbonate (2.0 mmol) was added. After the disappearance of the reagents (0.1–0.5 h; TLC monitoring), the K_2CO_3 was filtered off, the reaction solvent was evaporated under reduced pressure, and the crude mixture was purified by column chromatography with silica gel (cyclohexane/ethyl acetate mixtures) to afford the corresponding bis(hydrazone)-functionalized rhodanines **4a**–**4f**, which were crystallized from diethyl ether/petroleum ether (b.p. 40–60 °C).

Dimethyl 2,2′-[(3-Ethyl-4-oxo-2-thioxothiazolidine-5,5-diyl)bis(4-ethoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylate) (4a): White solid (887.2 mg, 79 % yield). M.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.13–1.23 (m, 9 H, 2 OCH$_2$*CH*$_3$, NCH$_2$*CH*$_3$), 1.87 (s, 3 H, CH$_3$), 1.99 (s, 3 H, CH$_3$), 3.76 (s, 3 H, OCH$_3$), 3.79 (s, 3 H, OCH$_3$), 4.02–4.12 (m, 7 H, CH, 2 O*CH*$_2$CH$_3$, N*CH*$_2$CH$_3$), 4.51 (br. s, 1 H, CH), 8.24 (br. s, 2 H, 2 NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.0 (q), 13.8 (q), 13.9 (q), 14.8 (q), 17.2 (q), 39.6 (t), 52.8 (q), 58.2 (s), 58.7 (d), 61.0 (d), 61.8 (t), 62.1 (t), 146.0 (s), 146.3 (s), 154.1 (s), 154.7 (s), 167.5 (s), 168.5 (s), 177.0 (s), 203.4 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3239, 1737, 1715, 1666 cm^{-1}. MS (ESI): *m*/*z* = 562.70 [M + H$^+$]. $C_{21}H_{31}N_5O_9S_2$ (561.6289): calcd. C 44.91, H 5.56, N 12.47; found C 45.04, H 5.59, N 12.35.

Dimethyl 2,2′-[(4-Oxo-3-phenyl-2-thioxothiazolidine-5,5-diyl)bis(4-ethoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylate) (4b): White solid (1.03 g, 85 % yield). M.p. 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23–1.36 (m, 6 H, 2 OCH$_2$*CH*$_3$), 1.84 (s, 3 H, CH$_3$), 2.08 (s, 3 H, CH$_3$), 3.73 (br. s, 3 H, CH$_3$), 3.73 (s, 3 H, OCH$_3$), 4.18 (s, 1 H, CH), 4.19–4.30 (m, 4 H, 2 O*CH*$_2$CH$_3$), 4.67 (br. s, 1 H, CH), 7.43–7.55 (m, 5 H, Ar), 7.98 (br. s, 1 H, NH), 8.17 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 14.4 (q), 14.6 (q), 17.5 (q), 52.7 (q), 52.8 (q), 53.0 (q), 53.1 (q), 58.1 (s), 58.9 (d), 59.0 (d), 62.1 (t), 128.2 (d), 128.3 (d), 129.3 (d), 136.0 (d), 145.4 (s), 146.0 (s), 153.3 (s), 153.4 (s), 154.1 (s), 168.4 (s), 169.4 (s), 171.1 (s), 204.0 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3241, 3160, 1741, 1720, 1690 cm^{-1}. MS (ESI): *m*/*z* = 608.72 [M – H$^+$]. $C_{25}H_{31}N_5O_9S_2$ (609.6717): calcd. C 49.25, H 5.13, N 11.49; found C 49.14, H 5.10, N 11.65.

Diethyl 2,2′-[(4-Oxo-3-phenyl-2-thioxothiazolidine-5,5-diyl)bis(4-methoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylate) (4c): White solid (1.12 g, 92 % yield). M.p. 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28–1.37 (m, 6 H, 2 OCH$_2$*CH*$_3$), 1.85 (s, 3 H, CH$_3$), 2.08 (s, 3 H, CH$_3$), 3.74 (s, 3 H, OCH$_3$), 3.74 (s, 3 H, OCH$_3$), 4.18 (s, 1 H, CH), 4.19–4.31 (m, 4 H, 2 O*CH*$_2$CH$_3$), 4.69 (br. s, 1 H, CH), 7.44–7.56 (m, 5 H, Ar), 7.80 (br. s, 1 H, NH), 7.95 (br. s, H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 14.6 (q), 15.2 (q), 17.5 (q), 52.8 (q), 53.1 (q), 58.2 (s), 62.1 (t), 62.3 (d), 65.8 (d), 128.3 (d), 129.3 (d), 129.4 (d), 136.0 (s), 146.0 (s), 153.1 (s), 153.9 (s), 168.4 (s), 169.4 (s), 171.2 (s), 204.0 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3234, 3159, 3127, 1741, 1701 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{32}N_5O_9S_2$ [M + H]$^+$ 610.1641; found 610.1641. MS (ESI): *m*/*z* = 610.55 [M + H$^+$]. $C_{25}H_{31}N_5O_9S_2$ (609.6717): calcd. C 49.25, H 5.13, N 11.49; found C 49.12, H 5.11, N 11.62.

Di-*tert*-butyl 2,2′-[(4-Oxo-3-phenyl-2-thioxothiazolidine-5,5-diyl)bis(4-ethoxy-4-oxobutan-3-yl-2-ylidene)]bis(hydrazinecarboxylate) (4d): White solid (1.29 g, 93 % yield). M.p. 138–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23–1.27 (m, 6 H, 2 OCH$_2$*CH*$_3$), 1.51 [s, 9 H, C(CH$_3$)$_3$], 1.56 [s, 9 H, C(CH$_3$)$_3$], 1.84 (s, 3 H, CH$_3$), 2.09 (s, 3 H, CH$_3$), 4.11 (s, 1 H, CH), 4.17–4.23 (m, 4 H, 2 O*CH*$_2$CH$_3$), 4.67 (br. s, 1 H, CH), 7.45–7.56 (m, 5 H, Ar), 7.65 (br. s, 1 H, NH), 7.77 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.9 (q), 14.0 (q), 14.5 (q), 17.6 (q), 28.2 (q), 28.4 (q), 58.2 (s), 59.1 (d), 59.2 (d), 61.9 (t), 62.1 (t), 62.2 (t), 81.5 (s), 81.7 (s), 128.4 (d), 129.3 (d), 136.2 (s), 145.3 (s), 151.9 (s), 152.6 (s), 168.0 (s), 169.0 (s), 177.4 (s), 204.4 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3328, 3225, 1724, 1746, 1700 cm^{-1}. MS (ESI): *m*/*z* = 694.00 [M + H$^+$]. $C_{31}H_{43}N_5O_9S_2$ (693.8312): calcd. C 53.66, H 6.25, N 10.09; found C 53.78, H 6.29, N 10.02.

Diethyl 2,2′-{[3-(4-Chlorophenyl)-4-oxo-2-thioxothiazolidine-5,5-diyl]bis(4-methoxy-4-oxobutan-3-yl-2-ylidene)}-bis(hydrazinecarboxylate) (4e): White solid (1.13 g, 88 % yield). M.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.29–1.37 (m, 6 H, 2 OCH$_2$*CH*$_3$), 1.83 (s, 3 H, CH$_3$), 2.09 (s, 3 H, CH$_3$), 3.73 (s, 3 H, OCH$_3$), 3.74 (s, 3 H, OCH$_3$), 4.17 (s, 1 H, CH), 4.20–4.33 (m, 4 H, 2 O*CH*$_2$CH$_3$), 4.68 (s, 1 H, CH), 7.40 (d, *J* = 8.4 Hz, 2 H, Ar), 7.51 (d, *J* = 9.2 Hz, 2 H, Ar), 7.84 (br. s, 1 H, NH), 7.98 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 14.4 (q), 14.5 (q), 15.2 (q), 17.6 (q), 52.9 (q), 53.2 (q), 58.2 (s), 59.0 (d), 62.1 (t), 65.8 (d), 129.7 (d), 129.8 (d), 134.5 (s), 135.4 (s), 145.8 (s), 153.1 (s), 155.8 (s), 168.5 (s), 169.5 (s), 177.1 (s), 203.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3332, 3209, 1718, 1752, 1698 cm^{-1}. MS (ESI): *m*/*z* = 643.31 [M – H$^+$]. $C_{25}H_{30}ClN_5O_9S_2$ (644.1168): calcd. C 46.62, H 4.69, N 10.87; found C 46.75, H 4.71, N 10.73.

Di-*tert*-butyl 2,2′-{[3-(4-Methoxyphenyl)-4-oxo-2-thioxothiazolidine-5,5-diyl]bis(4-ethoxy-4-oxobutan-3-yl-2-ylidene)}-bis(hydrazinecarboxylate) (4f): White solid (1.34 g, 93 % yield). M.p. 169–171 °C (dec.) ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21–1.77 (m, 6 H, 2 OCH$_2$*CH*$_3$), 1.51 [s, 9 H, C(CH$_3$)$_3$], 1.55 [s, 9 H, C(CH$_3$)$_3$], 1.83 (s, 3 H, CH$_3$), 2.08 (s, 3 H, CH$_3$), 3.84 (s, 3 H, OCH$_3$), 4.09 (s, 1 H, CH), 4.16–4.23 (m, 4 H, 2 O*CH*$_2$CH$_3$), 4.66 (s, 1 H, CH), 7.03 (d, *J* = 9.2 Hz, 2 H, Ar), 7.37 (d, *J* = 8.4 Hz, 2 H, Ar), 7.64 (br. s, 1 H, NH), 7.75 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q), 14.0 (q), 14.5 (q), 17.6 (q), 28.2 (q), 28.4 (q), 55.4 (q), 58.2 (s), 59.2 (d), 61.9 (t), 61.9 (t), 62.2 (t), 65.8 (d), 81.5 (s), 81.7 (s), 114.6 (d), 128.7 (s), 129.4 (d), 145.4 (s), 151.8 (s), 160.0 (s), 168.0 (s), 169.0 (s), 177.5 (s), 204.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3246, 3150, 3109, 1754, 1693 cm^{-1}. MS (ESI): *m*/*z* = 724.67 [M + H$^+$]. $C_{32}H_{45}N_5O_{10}S_2$ (723.8572): calcd. C 53.10, H 6.27, N 9.68; found C 53.01, H 6.26, N 9.78.

General Procedure for the Synthesis of 2,3,5,6-Tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones 6a, 6c–6e, 6j, and 6l by Starting from 4a–4f (Path A): To a magnetically stirred solution of bis(hydrazone)-functionalized rhodanines **4a**–**4f** (1.0 mmol) in THF (6 mL) heated at 55 °C in an oil bath, potassium carbonate (5.0 mmol) was added. The flask was kept open to remove CS_2 by

evaporation (b.p. 49.3 °C). After the disappearance of products **4** (2.0–5.0 h; TLC monitoring), the K_2CO_3 was filtered off, the reaction solvent was evaporated under reduced pressure, and the crude mixture was purified by column chromatography with silica gel (cyclohexane/ethyl acetate mixtures) to afford the corresponding 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6a**, **6c**–**6e**, **6j**, and **6l**, which were crystallized from diethyl ether/petroleum ether (b.p. 40–60 °C).

General Procedure for the Synthesis of 2,3,5,6-Tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones 6a–6l in a One-Pot Procedure (Path B): To a magnetically stirred solution of 1,2-diaza-1,3-dienes **1a**–**1g** (2.1 mmol) and 3-ethyl-, 3-phenyl-, 3-(4-chlorophenyl)-, or 3-(4-methoxyphenyl)-2-thioxothiazolidin-4-ones **2a**–**2d** (1.0 mmol) in THF (5 mL) heated at 55 °C in an oil bath, potassium carbonate (5.0 mmol) was added. The flask was kept open to remove CS_2 by evaporation. After the disappearance of the reagents (1.0–5.0 h; TLC monitoring), the K_2CO_3 was filtered off, the reaction solvent was evaporated under reduced pressure, and the crude mixture was purified by column chromatography with silica gel (cyclohexane/ethyl acetate mixtures) to afford the corresponding 2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-triones **6a**–**6l**, which were crystallized from diethyl ether/petroleum ether (b.p. 40–60 °C).

Methyl 2-(1-{2-Ethyl-5-[(methoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6a): Pale yellow powder (149.7 mg, 38 % yield, Path A; 239.8 mg, 61 % yield, Path B). M.p. 235–237 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 2.16 (s, 3 H, CH_3), 2.79 (s, 3 H, CH_3), 3.68 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 3.83 (s, 6 H, 2 OCH_3), 7.60 (br. s, 1 H, NH), 8.16 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.4 (q), 14.4 (q), 15.6 (q), 33.4 (t), 53.2 (q), 54.2 (q), 105.7 (s), 125.4 (s), 137.2 (s), 142.5 (s), 152.2 (s), 156.2 (s), 161.0 (s), 164.0 (s), 165.5 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3331, 3239, 1753, 1721, 1672 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}N_5O_7$ [M + H]$^+$ 394.1363; found 394.1363. MS (ESI): m/z = 394.11 [M + H$^+$]. $C_{16}H_{19}N_5O_7$ (393.1284): calcd. C 48.85, H 4.87, N 17.80; found C 48.94, H 4.85, N 17.68.

***tert*-Butyl 2-(1-{5-[(*tert*-Butoxycarbonyl)amino]-2-ethyl-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]-pyridin-7-yl}ethylidene)hydrazinecarboxylate (6b):** Pale yellow powder (277.7 mg, 58 % yield, Path B). M.p. 218–220 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.50 [s, 18 H, 2 $C(CH_3)_3$], 2.13 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3), 3.67 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 7.38 (br. s, 1 H, NH), 7.89 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.4 (q), 14.4 (q), 15.6 (q), 28.0 (q), 28.2 (q), 33.3 (t), 81.4 (s), 83.8 (s), 105.1 (s), 125.6 (s), 136.7 (s), 141.4 (s), 152.1 (s), 154.5 (s), 160.9 (s), 164.2 (s), 165.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3358, 3190, 1735, 1718, 1678 cm^{-1}. MS (ESI): m/z = 476.38 [M – H$^+$]. $C_{22}H_{31}N_5O_7$ (477.5108): calcd. C 55.34, H 6.54, N 14.67; found C 55.22, H 6.50, N 14.78.

Methyl 2-(1-{5-[(Methoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6c): Pale yellow powder (209.3 mg, 37 % yield, Path A; 340.2 mg, 60 % yield, Path B). M.p. 169–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.16 (s, 3 H, CH_3), 2.83 (s, 3 H, CH_3), 3.82 and 3.85 (2 s, 6 H, 2 OCH_3), 7.34–7.37 (m, 2 H, Ph), 7.39–7.43 (m, 1 H, Ph), 7.47–7.51 (m, 2 H, Ph), 7.80 (br. s, 1 H, NH), 8.20 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5 (q), 14.6 (q), 15.5 (q), 15.6 (q), 53.3 (q), 54.1 (q), 54.2 (q), 105.1 (s), 125.8 (s), 126.5 (d), 126.6 (d), 129.1 (d), 131.2 (s), 136.7 (s), 142.5 (s), 153.5 (s), 156.2 (s), 161.0 (s), 163.3 (s), 164.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3352, 3195, 1738, 1722, 1681 cm^{-1}. MS (ESI): m/z = 442.27 [M + H$^+$]. $C_{20}H_{19}N_5O_7$ (441.3942): calcd. C 54.42, H 4.34, N 15.87; found C 54.57, H 4.38, N 15.76.

Ethyl 2-(1-{5-[(Ethoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6d): Pale yellow powder (165.2 mg, 35 % yield, Path A; 258.6 mg, 55 % yield, Path B). M.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28–1.34 (m, 6 H, 2 OCH_2CH_3), 2.16 (s, 3 H, CH_3), 2.84 (s, 3 H, CH_3), 4.25–4.33 (m, 4 H, 2 OCH_2CH_3), 7.34–7.37 (m, 2 H, Ph), 7.39–7.42 (m, 1 H, Ph), 7.47–7.51 (m, 2 H, Ph), 7.58 (br. s, 1 H, NH), 8.04 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (q), 14.5 (q), 14.6 (q), 15.6 (q), 62.1 (t), 63.6 (t), 105.1 (s), 125.8 (s), 126.5 (d), 128.5 (d), 129.1 (d), 131.2 (s), 136.7 (s), 142.4 (s), 153.6 (s), 155.8 (s), 161.0 (s), 163.4 (s), 164.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3343, 3239, 1722, 1675, 1631 cm^{-1}. MS (ESI): m/z = 470.15 [M + H$^+$]. $C_{22}H_{23}N_5O_7$ (469.4473): calcd. C 56.29, H 4.94, N 14.92; found C 56.36, H 4.96, N 14.81.

***tert*-Butyl 2-(1-{5-[(*tert*-Butoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6e):** Pale yellow powder (216.2 mg, 41 % yield, Path A; 346.1 mg, 66 % yield, Path B). M.p. 220–222 °C (dec.). ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.45 and 1.48 [2 s, 18 H, 2 $C(CH_3)_3$], 2.06 (s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), 7.38–7.40 (m, 2 H, Ph), 7.44–7.46 (m, 1 H, Ph), 7.49–7.53 (m, 2 H, Ph), 9.93 (br. s, 1 H, NH), 10.23 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 14.0 (q), 16.9 (q), 27.8 (q), 28.0 (q), 79.4 (s), 81.4 (s), 104.2 (s), 125.9 (s), 127.4 (d), 128.3 (d), 128.7 (d), 131.7 (s), 135.6 (s), 142.7 (s), 152.4 (s), 152.7 (s), 154.2 (s), 160.0 (s), 163.3 (s), 164.7 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3314, 3253, 1725, 1712, 1677 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{32}N_5O_7$ [M + H]$^+$ 526.2302; found 526.2302. MS (ESI): m/z = 524.38 [M – H$^+$]. $C_{26}H_{31}N_5O_7$ (525.5536): calcd. C 59.42, H 5.95, N 13.33; found C 59.49, H 5.99, N 13.20.

Ethyl 2-(1-{4-Butyl-5-[(ethoxycarbonyl)amino]-1,3,6-trioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}pentylidene)hydrazinecarboxylate (6f): Pale yellow powder (350.8 mg, 63 % yield, Path B). M.p. 194–196 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85–0.98 (m, 8 H, alkyl), 1.24–1.39 (m, 8 H, alkyl), 1.56–1.74 (m, 4 H, alkyl), 2.48–2.63 (m, 2 H, alkyl), 2.71–3.09 (m, 2 H, alkyl), 4.21–4.32 (m, 4 H, 2 OCH_2CH_3), 7.08 (br. s, 1 H, NH), 7.37–7.41 (m, 3 H, Ph), 7.47–7.50 (m, 2 H, Ph), 8.06 and 8.27 (2 br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.6 (q), 13.7 (q), 14.3 (q), 14.5 (q), 22.7 (t), 23.0 (t), 27.0 (t), 27.9 (t), 29.7 (t), 30.7 (t), 63.6 (t), 104.7 (s), 126.4 (s), 126.5 (d), 128.5 (d), 129.1 (d), 131.2 (s), 137.5 (s), 139.3 (s), 156.0 (s), 157.6 (s), 161.5 (s), 163.4 (s), 164.5 (s), 165.3 ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3348, 3192, 1729, 1721, 1680 cm^{-1}. MS (ESI): m/z = 552.37 [M – H$^+$]. $C_{28}H_{35}N_5O_7$ (553.6068): calcd. C 60.75, H 6.37, N 12.65; found C 60.62, H 6.33, N 12.79.

Benzyl 2-[1-(5-{[(Benzyloxy)carbonyl]amino}-4-methyl-1,3,6-trioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl)-ethylidene]hydrazinecarboxylate (6g): Pale yellow powder (253.8 mg, 43 % yield, Path B). M.p. 199–201 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.12 (s, 3 H, CH_3), 2.80 (s, 3 H, CH_3), 5.22 and 5.25 (2 s, 4 H, 2 OCH_2Ph), 7.34–7.51 (m, 15 H, 3 Ph), 7.64 (s, 1 H, NH), 8.12 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 14.8 (q), 27.8 (q), 67.8 (T), 69.1 (s), 105.1 (s), 126.4 (s), 126.5 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.6 (d), 128.7 (d), 128.8 (d), 129.1 (d), 129.2 (s), 131.2 (s), 134.7 (s), 136.8 (s), 142.5 (s), 153.5 (s), 153.5 (s), 155.5 (s), 160.9 (s), 163.3 (s), 164.6 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3331, 3240, 1738, 1725, 1670 cm^{-1}. MS (ESI): m/z = 592.12 [M + H$^+$]. $C_{32}H_{27}N_5O_7$ (593.5861): calcd. C 64.75, H 4.58, N 11.80; found C 64.66, H 4.54, N 11.88.

Methyl 2-(1-{2-(4-Chlorophenyl)-5-[(methoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]-

pyridin-7-yl}ethylidene)hydrazinecarboxylate (6h): Pale yellow powder (220.2 mg, 46 % yield, Path B). M.p. 221–222 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.13 (s, 3 H, CH_3), 2.80 (s, 3 H, CH_3), 3.79 and 3.83 (2 s, 6 H, 2 OCH_3), 7.32 (d, J = 8.8 Hz, 2 H, Ph), 7.45 (d, J = 8.8 Hz, 2 H, Ph), 8.34 (s, 1 H, NH), 8.61 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 14.7 (q), 15.5 (q), 15.6 (q), 53.1 (q), 53.3 (q), 54.1 (q), 54.3 (q), 104.9 (s), 126.0 (s), 127.6 (d), 129.3 (d), 129.6 (s), 134.4 (s), 136.5 (s), 142.2 (s), 153.8 (s), 156.2 (s), 160.9 (s), 163.0 (s), 164.4 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3325, 3239, 1752, 1735, 1718, 1670 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{19}ClN_5O_7$ $[M + H]^+$ 476.0973; found 476.0973. MS (ESI): m/z = 476.10 $[M + H^+]$. $C_{20}H_{18}ClN_5O_7$ (475.8392): calcd. C 50.48, H 3.81, N 14.72; found C 50.59, H 3.82, N 14.65.

***tert*-Butyl 2-(1-{5-[(*tert*-Butoxycarbonyl)amino]-2-(4-chlorophenyl)-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6i):** Pale yellow powder; (284.8 mg, 51 % yield, Path B). M.p. 171–173 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.49 [s, 18 H, 2 $C(CH_3)_3$], 2.13 (s, 3 H, CH_3), 2.82 (s, 3 H, CH_3), 7.33 (d, J = 8.8 Hz, 2 H, Ph), 7.45 (d, J = 8.8 Hz, 2 H, Ph), 7.48 (br. s, 1 H, NH), 7.86 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5 (q), 14.7 (q), 15.5 (q), 15.7 (q), 27.9 (q), 28.0 (q), 28.2 (q), 28.3 (q), 81.5 (s), 83.9 (s), 104.4 (s), 126.1 (s), 127.8 (d), 127.8 (d), 129.2 (d), 129.3 (d), 129.8 (d), 134.2 (s), 136.1 (s), 141.7 (s), 152.1 (s), 153.7 (s), 154.4 (s), 160.9 (s), 163.2 (s), 164.6 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3328, 3205, 1732, 1718, 1685 cm^{-1}. MS (ESI): m/z = 558.30 $[M - H^+]$. $C_{26}H_{30}ClN_5O_7$ (559.9987): calcd. C 55.76, H 5.40, N 12.51; found C 55.84, H 5.44, N 12.53.

Ethyl 2-(1-{2-(4-Chlorophenyl)-5-[(ethoxycarbonyl)amino]-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]-pyridin-7-yl}ethylidene)hydrazinecarboxylate (6j): Pale yellow powder (194.8 mg, 39 % yield, Path A; 293.7 mg, 58 % yield, Path B). M.p. 177–180 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23–1.29 (m, 6 H, 2 OCH_2CH_3), 2.13 (s, 3 H, CH_3), 2.80 (s, 3 H, CH_3), 4.12–4.33 (m, 4 H, 2 OCH_2CH_3), 7.32 (d, J = 8.0 Hz, 2 H, Ph), 7.44 (d, J = 8.0 Hz, 2 H, Ph), 7.93, 8.03, 8.16 and 8.33 (4 br. s, 2 H, 2 NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14. 1 (q), 14.3 (q), 14.5 (q), 14.7 (q), 60.4 (t), 63.5 (t), 104.8 (s), 126.0 (s), 127.8 (d), 129.3 (d), 129.8 (s), 134.3 (s), 136.4 (s), 142.6 (s), 153.9 (s), 155.8 (s), 158.8 (s), 161.0 (s), 163.2 (s), 164.5 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3325, 3200, 1731, 1714, 1680 cm^{-1}. MS (ESI): m/z = 502.76 $[M - H^+]$. $C_{22}H_{22}ClN_5O_7$ (503.8924): calcd. C 52.44, H 4.40, N 13.90; found C 52.51, H 4.38, N 14.01.

Ethyl 2-(1-{5-[(Ethoxycarbonyl)amino]-2-(4-methoxyphenyl)-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6k): Pale yellow oil; (295.4 mg, 59 % yield, Path B). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.26 (q, J = 7.2 Hz, 6 H, 2 OCH_2CH_3), 2.12 (s, 3 H, CH_3), 2.78 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.22–4.28 (m, 4 H, 2 OCH_2CH_3), 6.97 (d, J = 8.8 Hz, 2 H, Ph), 7.25 (d, J = 8.8 Hz, 2 H, Ph), 8.14 (br. s, 1 H, NH), 8.30 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14. 2 (q), 14.4 (q), 14.4 (q), 15.6 (q), 60.4 (t), 55.4 (q), 60.3 (t), 63.3 (t), 105.0 (s), 114.4 (d), 123.8 (s), 125.8 (s), 127.8 (d), 136.6 (s), 142.7 (s), 153.4 (s), 155.7 (s), 159.4 (s), 161.0 (s), 163.6 (s), 165.0 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3305, 3148, 1737, 1720, 1701 cm^{-1}. MS (ESI): m/z = 498.44 $[M - H^+]$. $C_{23}H_{25}N_5O_8$ (499.4733): calcd. C 55.31, H 5.05, N 14.02; found C 55.22, H 5.03, N 14.11.

***tert*-Butyl 2-(1-{5-[(*tert*-Butoxycarbonyl)amino]-2-(4-methoxyphenyl)-4-methyl-1,3,6-trioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7-yl}ethylidene)hydrazinecarboxylate (6l):** Pale yellow solid; (338.9 mg, 61 % yield, Path A; 355.1 mg, 64 % yield, Path B). M.p. 171–173 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.47 [s, 18 H, 2 $C(CH_3)_3$], 2.12 (s, 3 H, CH_3), 2.78 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 6.97 (d, J = 9.2 Hz, 2 H, Ph), 7.26 (d, J = 9.2 Hz, 2 H, Ph), 7.73 (br. s, 1 H, NH), 7.96 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 15.7 (q), 27.9 (q), 28.2 (q), 55.4 (q), 81.3 (s), 83.4 (s), 104.6 (s), 114.3 (d), 123.9 (s), 125.7 (s), 127.8 (d), 136.4 (s), 141.8 (s), 152.2 (s), 153.3 (s), 154.5 (s), 159.4 (s), 161.0 (s), 163.8 (s), 165.2 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3302, 3150, 2982, 1739, 1719, 1709 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{33}N_5O_8$ $[M + H]^+$ 556.2407; found 556.2407. MS (ESI): m/z = 554.44 $[M - H^+]$. $C_{27}H_{33}N_5O_8$ (555.5796): calcd. C 58.37, H 5.99, N 12.61; found C 58.50, H 6.01, N 12.52.

General Procedure for the Synthesis of 7-Acetyl-5-amino-4-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (7a) by Starting from 6e: To a magnetically stirred solution of **6e** (1.0 mmol) in acetone/water (4.5:0.5 mL) at room temperature, Amberlyst 15H (500 mg) was added. After the disappearance of product **6e** (3.0 h; TLC monitoring), Amberlyst 15H was filtered off, the reaction solvent was evaporated under reduced pressure, and the crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate mixtures) to afford **7a**, which was crystallized from diethyl ether/petroleum ether (b.p. 40–60 °C).

7-Acetyl-5-amino-4-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-(2*H*,5*H*)-trione (7a): White powder (257.8 mg, 83 % yield). M.p. 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.62 (s, 3 H, CH_3), 2.96 (s, 3 H, CH_3), 5.05 (br. s, 2 H, NH_2), 7.36–7.51 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15. 1 (q), 31.0 (q), 104.2 (s), 126.4 (d), 128.6 (d), 129.1 (d), 131.7 (s), 131.1 (s), 134.0 (s), 151.4 (s), 159.2 (s), 163.5 (s), 164.9 (s), 197.5 (s) ppm. IR (nujol): $\tilde{\nu}_{max}$ = 3300, 3201, 1720, 1685, 1615 cm^{-1}. MS (ESI): m/z = 312.14 $[M + H^+]$. $C_{16}H_{13}N_3O_4$ (311.2921): calcd. C 61.73, H 4.21, N 13.50; found C 61.85, H 4.25, N 13.39.

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