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Investigation of the regioselectivity of the Hurd–Mori reaction for the formation of bicyclic 1,2,3-thiadiazoles

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This work is dedicated to Professor Saverio Florio on the occasion of his 70th birthday

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ABSTRACT

A series of new pyrrolo[*d*][1,2,3]thiadiazole carboxylates and 5,6-dihydro-4*H*-cyclopenta[*d*][1,2,3]thiadiazoles has been synthesized via the Hurd–Mori reaction. The regioselectivity of the cyclization has been studied and trends were established to predict the cyclization direction to afford bicyclic 1,2,3-thiadiazoles. Effects promoting and disfavoring the reaction have also been investigated to guide the synthesis of scaffolds of this type.

1. Introduction

Structures containing a 1,2,3-thiadiazole are promising targets in medicinal and agrochemical applications.[1] Most notably, interest in the aryl- or heteroaryl-fused bicyclic thiadiazole motif arose when benzo[*d*][1,2,3]thiadiazole-7-carboxylic acid and its methyl carbothioate—the latter being commercialized as Actigard® (BION®)—were identified as a class of compounds known as plant activators.[2,3] These substances are capable of stimulating a higher organism, such as a crop, to develop an otherwise not observed immune response when confronted with pathogens. This phenomenon is commonly referred to as 'systemic acquired resistance'.[4] Previously, we could show that various methyl thieno[2,3-*d*][1,2,3]-thiadiazole-6-carboxylates act as active bioisosters of Actigard® (Fig. 1).[5]

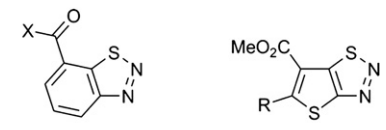

Figure 1. Systemic acquired resistance-inducing bicyclic 1,2,3-thiadizoles.

Access to 1,2,3-thiadiazoles in general can be gained via a variety of methods, and the topic has been extensively reviewed.[6] Among these pathways are the cycloaddition of diazoalkanes to thiocarbonyl compounds (Pechmann–Nold synthesis[7]) and the cycloaddition of α-diazo thiocarbonyl precursors (Wolff synthesis[8]). However, the most versatile route to enable the synthesis of fused thiadiazoles of the general structure **III** starts from the corresponding monocyclic carbonyl or thiocarbonyl materials **I**. The bicyclic system is then formed by incorporating both nitrogen atoms from a hydrazine-derived reagent (such as ethyl hydrazinecarboxylate or tosylhydrazide) and the sulfur atom from an electrophile (in many cases thionyl chloride) used in excess. This method is known as the Hurd–Mori cyclization (Scheme 1).[9] Despite its quite universal applicability, including a recent solid-phase adaptation,[10] the success of the transformation crucially depends on the functional decoration of the starting compounds. In particular, the regioselectivity of the ring-closing step is heavily influenced by both electronic and steric factors.

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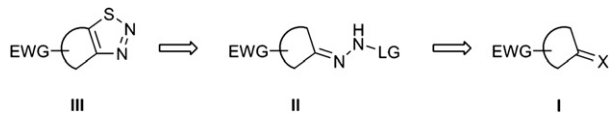
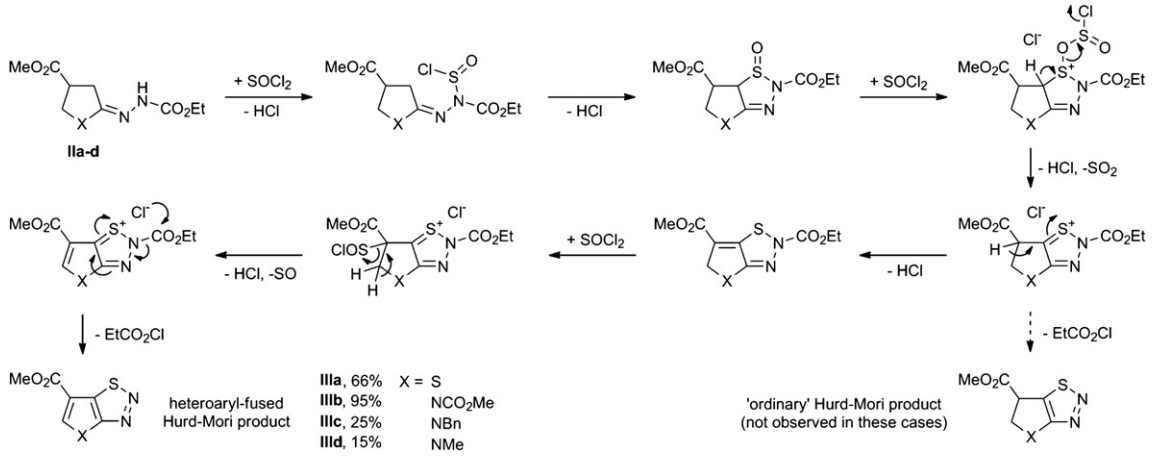


Scheme 1. Hurd–Mori retrosynthetic analysis.

These effects, exerted by the various structural elements, may oppose each other and questions arise as to which aspect will dominate. The reaction involves nucleophilic attack of the α-carbon of hydrazone **II** to the electron deficient sulfur moiety and subsequent cyclization toward formation of a 1,2,3-thiadiazolin-1-one as key intermediate (Scheme 2).[11] Therefore, the ease of enolization under the applied reaction conditions is the most important directing factor for substrates where enolization can occur in two different directions.[12] However, the electronic influence of such a substituent can be overruled if a neighboring group is sterically demanding.[13] In contrast to this, the *E*/*Z* ratio of the hydrazone at equilibrium was found to be unimportant and the nature of the leaving group had only a minor, albeit noticeable, effect on the cyclization direction.[14,15]

(−5 to −20 °C). Our earlier results[18] showed that the efficiency of the cyclization was dramatically affected by the electronic properties of the 2-hydrazonopyrrolidine substrate species (Scheme 2). Excellent yield of 95% was observed in the case where the strongly electron withdrawing methoxycarbonyl group at the pyrrolidine nitrogen was present (**IIb**), and poor amounts of isolated material in the case of *N*-substituents such as benzyl or the even donating methyl group (**IIc**: 25% and **IId**: 15%).[18]

We now found that if Boc is used as the *N*-protecting group **2** in place of $MeCO_2$, a comparable yield of 82% of the thiadiazole **3** was obtainable (Scheme 3). In agreement with the aforementioned effect we also observed that retaining the *N*-methoxycarbonyl group but removing the ester from the 4-position instead, as in compound **6**, led to lower yields also, thereby giving the *N*-methoxycarbonyl-protected parent compound 4*H*-pyrrolo[2,3-*d*][1,2,3]thiadiazole **7** in moderate 29% yield. These results make it clear already that substituent-induced electron deficiency promotes successful Hurd–Mori cyclization. It shall also be pointed out that the choice of the *N*-protecting group is not trivial, as the Boc-group can be removed more smoothly but, when placed on different regioiso-



Scheme 2. Route to reported 1,2,3-thiadiazole target structures and proposed mechanistic rationale for aromatization, giving rise to fused 1,2,3-thiadiazoles.

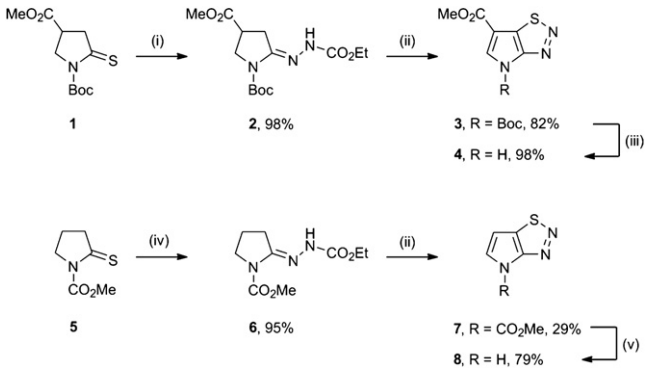
In an earlier contribution we demonstrated the use of the method in the synthesis of **IIIa** from hydrazinecarboxylate **IIa** directly, i.e., with complete aromatization occurring concomitantly with ring closure (Scheme 2).[16] Our findings indicated that a more complex process than simple oxidation of a dihydro intermediate is involved, which allowed us to suggest a mechanism for this transformation to account for the complete aromatization of the product species as well as for a halogenated side product formed under certain reaction conditions.[16,17]

The biological activity found in these compounds then led us to pursue this strategy in a follow-up approach to the analogous pyrrolo[2,3-*d*][1,2,3]thiadiazole-6-carboxylates (**IIIb**–**d**).[18] We were thus prompted to a systematic investigation to allow for selectivity and efficiency predictions of target structures of this type and continued to study the scope and limitations of the method in the quest for potential biologically active analogs. Therefore, we present the synthesis of hitherto unreported pyrrolo[*d*][1,2,3]thiadiazole carboxylates and 5,6-dihydro-4*H*-cyclopenta[*d*][1,2,3]thiadiazoles, in which case it was possible to draw conclusions as to the applicability of the Hurd–Mori route for the desired targets and compare it to the synthesis of similar compounds that we had established previously.

2. Results and discussion

The general reaction conditions involved dropwise addition of the precursors **II** to 7 equiv of $SOCl_2$ in CH_2Cl_2 at low temperature

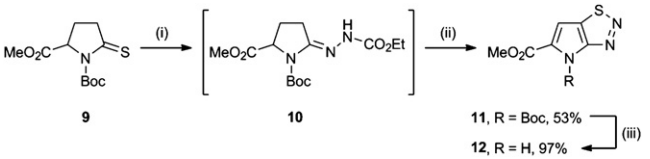
meric substrates, did not withstand the acidic conditions of the Hurd–Mori step in every case even though the temperature conditions were milder than in the synthesis of **3** (i.e., in case of **16**: addition at −20 °C and subsequent reaction at −16 °C, Scheme 5).



Scheme 3. Reagents and conditions: (i) $EtCO_2NHNH_2$, CH_2Cl_2, reflux, 21 h; (ii) $SOCl_2$, CH_2Cl_2, −10 to −5 °C, dropwise addition 1 h; to rt, overnight; (iii) CF_3CO_2H, CH_2Cl_2, reflux 5 h; (iv) $EtCO_2NHNH_2$, CH_2Cl_2, rt, 72 h; (v) KOH, MeOH, reflux, 16 h.

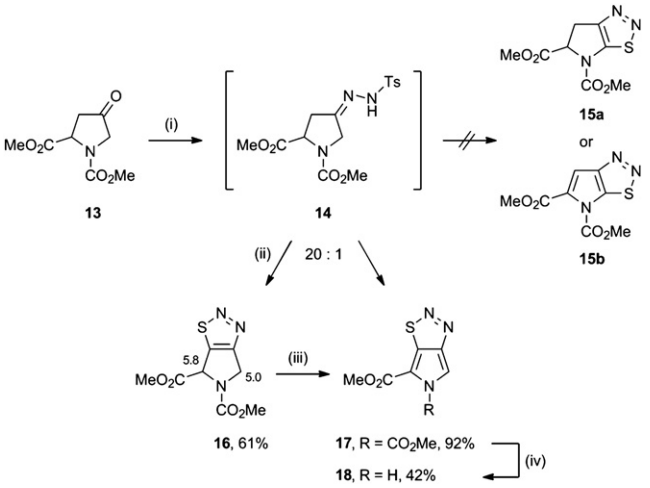
The regioisomer **11** (Scheme 4) with the ester group adjacent to the pyrrolo-*N* could be synthesized starting from thiolactam **9**. The carbazate **10** formed with ethyl hydrazinecarboxylate could be used for the Hurd–Mori cyclization without purification of this

intermediate. In the presence of an electron withdrawing group, significantly more amount of the desired material (53%) was obtained compared to the preparation of **7**. The use of Boc proved to be preferable to $MeCO_2$ protection because of its more facile introduction (catalyzed by DMAP/Et_3N) prior to the key step of the reaction sequence and the milder conditions sufficient for its removal.



Scheme 4. Reagents and conditions: (i) $EtCO_2NHNH_2$, CH_2Cl_2, reflux, 72 h; (ii) $SOCl_2$, CH_2Cl_2, −10 to −5 °C, dropwise addition 1 h; to rt, overnight; (iii) CF_3CO_2H, CH_2Cl_2, reflux, 5 h.

As already reported,[18] lactams needed to be converted into the corresponding thio compounds (with Lawesson's reagent) to allow for efficient reaction with ethyl hydrazine. This step was not required for keto-substrate **13** (in place of the amides corresponding to **1**, **5**, and **9**), obtained from the related alcohol via Collins oxidation, as starting material (Scheme 5). As in the sequences before, conversion with tosylhydrazide was immediately followed by treatment with $SOCl_2$ to effect thiadiazole formation. Since Hurd–Mori cyclization of precursor **13** can occur at both sides of the sp^2-carbon after hydrazone formation, a mixture of regioisomers had to be expected. Surprisingly, this cyclization gave only products **16** and **17** with sulfur incorporation at the distal site relative to the pyrrolidine nitrogen. However, in contrast to previous examples only a very small amount (3%) of the fully aromatized product **17** was obtained. Instead, the Hurd–Mori reaction gave compound **16** (61%, 20:1 ratio of **16** and **17**), predominantly. When compared to the other pyrrolo[*d*][1,2,3]thiadiazole carboxylates, it is evident that aromatization to **17** requires oxidation of two non-adjacent ring carbon atoms. It is known that similar structures such as benzo-fused pyrrole **19** (isoindole) are *ortho*-quinoid, but non-aromatic systems (Fig. 2).[19] Hence, it appears that the aromaticity of the 1,2,3-thiadiazole ring in **16** has to be disrupted as well in order to be transformed to **17**. Conversely, there is less gain in aromatization energy as the formation of **17** occurs, unlike in the case of **3**, **7**, and **11**. This also becomes apparent as the oxidation of **16**, although proceeding with 92% yield, is very slow



Scheme 5. Reagents and conditions: (i) $TsNHNH_2$, EtOH, rt, 16 h; (ii) $SOCl_2$, CH_2Cl_2, −20 °C, dropwise addition; then −16 °C, 4 h and rt, 5 h; (iii) DDQ, 1,4-dioxane, reflux, 40 h; (iv) aq HCl, reflux, 8 d; then acid removal ($CHCl_3$ azeotrope); then HCl/satd MeOH, 25 °C, 5 h and reflux, 2 h. ^{1}H NMR shifts (ppm) are indicated.

(40 h with DDQ in refluxing dioxane, making use of a known procedure[20]), indicating that compound **16** is very stable and therefore not converted further under Hurd–Mori conditions.

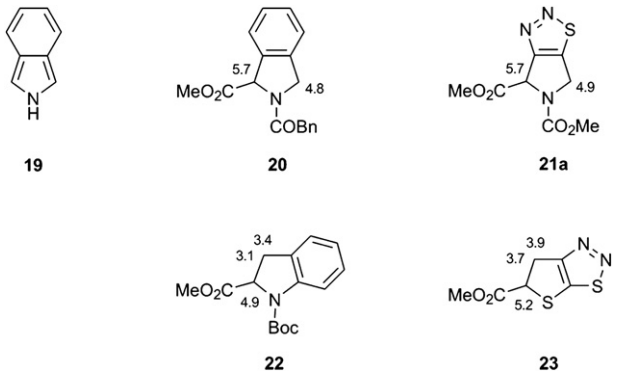
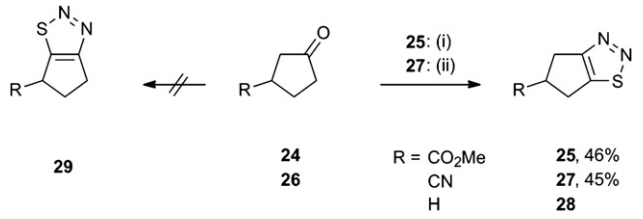


Figure 2. Related structures for shift comparison. ^{1}H NMR shifts (ppm) are indicated.

Incidentally, **16** is a 1,2,3-thiadiazole-fused (and therefore very rigid) proline derivative with its acid and amine functionalities protected, and scaffolds of this sort have received much attention in peptide and therapeutic research,[21] as well as in organocatalysis.[22] Its structure could be determined by comparison of the chemical shifts of the diastereotopic (het-)aryl-adjacent methylene group as well as the methine protons to data from analogous materials: **16** displayed congruent ^{1}H NMR characteristics with **21a**, which was formed unambiguously in a different Hurd–Mori cyclization (described below), as well as to compounds such as **20**.[23] In contrast, **15a** would display proton shifts similar to **23** from one of our previous studies,[17] as well as **22**.[24] The clear shift difference of approximately 1 ppm strongly supports our structure assignment (Scheme 5).

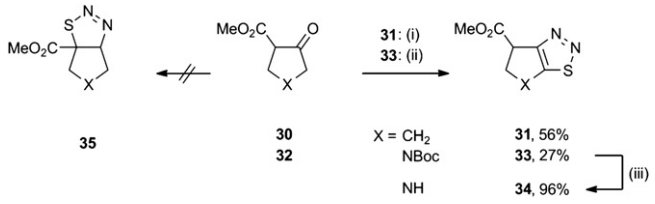
As mentioned before, the protecting group has to be chosen carefully. Removing the $MeCO_2$ from the pyrrolo-*N* gave an unsatisfactory yield of 42%, calling for an alternative. Therefore, the whole synthesis was attempted employing the Boc group for N-protection instead, but using otherwise identical reaction conditions. In this case we could identify only small amounts of *N*-Boc-deprotected products corresponding to **17** and **15b** (3% and 5%, respectively), along with traces of the expected Hurd–Mori product in analogy to **16**. Additionally, major amounts of unidentified decomposition products were formed. This suggests that the protecting group is cleaved prior to the cyclization. Obviously, the deprotected substrate does not undergo the Hurd–Mori reaction efficiently but is prone to decomposition under the applied reaction conditions.

At this point, the results obtained from the pyrrolo series can be compared to analogous compounds that lack the ring nitrogen. Structure **28** is a known compound prepared from the tosylhydrazone of cyclopentanone under Hurd–Mori conditions (neat $SOCl_2$, rt, 22%).[25] Repetition of this synthesis using milder conditions ($SOCl_2$, CH_2Cl_2, −10 °C, 28%) was comparable with our findings in the case of **7**. Placing an electron withdrawing group (methoxycarbonyl on **24** or cyano on **26**) at the carbon which is 1,3-related to the carbonyl group has the same effect of increasing the efficiency of the transformation (**25**: 46% and **27**: 45%; Scheme 6). Moreover, this comparison gives some more insight into the effects governing the regiochemistry of the ring formation: no isomeric products **29** were found. Consequently, ring closure is strongly directed away from the substituent. However, this behavior can be completely reversed by introducing the carbamate group into the starting material, as indicated by the exclusive formation of **16**, starting from **14**. Aromatization of the newly formed ring cannot occur in bicyclic systems such as **25**, **27**, and **28**, and only the Hurd–Mori reaction itself takes place.



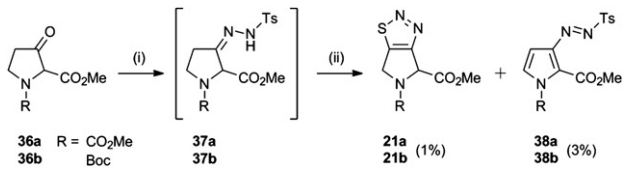
Scheme 6. Reagents and conditions: (i) $TsNHNH_2$, EtOH, rt, overnight; then solvent removal and $SOCl_2$, CH_2Cl_2, −10 °C, dropwise addition; to rt, 4 h; (ii) $TsNHNH_2$, CH_2Cl_2, rt, overnight; then solvent removal and $SOCl_2$, CH_2Cl_2, −10 °C, dropwise addition; to rt, 5 h.

It was therefore intriguing to study the course of the cyclization if the carbonyl group and the carbon atom bearing the methoxycarbonyl substituent are 1,2-related as in **30**, i.e., whether a stabilized enol would result in C–S bond-formation into the position of the carbon bearing the most acidic proton. However, ring closure proceeded neatly into the opposite direction (**31**, 56%), again with complete regioselectivity (Scheme 7). Notably, this is not only the kinetically favored isomer, but the angular ester group would also prevent aromatization in the thiadiazole ring. Consequently, it was not surprising that this transformation was hampered when the cyclization was forced in this manner to proceed toward a sterically demanding Boc-protected ring-nitrogen, as exemplified by the unfavorable conversion of **32** into **33** (yielding 27%). In accordance with the mechanism depicted in Scheme 2, no fully aromatized system was obtained, because this would require the elimination of a proton in **33** from the position where actually the NBoc group is in place.



Scheme 7. Reagents and conditions: (i) $TsNHNH_2$, EtOH, rt, 16 h; then solvent removal and $SOCl_2$, CH_2Cl_2, −10 °C, dropwise addition; then 0 °C, 64 h; (ii) $TsNHNH_2$, EtOH, rt, 16 h; then solvent removal and $SOCl_2$, CH_2Cl_2, −20 °C, dropwise addition; then −16 °C, 4 h and rt, 5 h; (iii) CF_3CO_2H, CH_2Cl_2, reflux 5 h.

Finally, we aimed for the synthesis of compound **21** from the appropriate precursors **36**. Hydrazone formation to **37** proceeded smoothly, but attempts to convert these intermediates into the corresponding thiadiazoles under conditions successful in the case of **16** and **33** produced only traces (1%) of the expected products of type **21** with either protecting group, accompanied by elementary sulfur precipitating from the reaction mixture and a small amount of oxidation product **38** (3%, Scheme 8). We believe that the direction of the enamine formation is preferred toward the ester group because the so formed double bond is in conjugation with the carbonyl C=O and cyclization to a thiadiazole product cannot take place. However, the isolation of **21a** helped to establish the structure of **16** as the regiochemistry of **21a** is unambiguous.



Scheme 8. Reagents and conditions: (i) $TsNHNH_2$, EtOH, rt, 16 h; (ii) $SOCl_2$, CH_2Cl_2, −20 °C, dropwise addition; then −16 °C, 4 h and rt, 5 h.

3. Conclusions

The results obtained within this study underline the importance of systematic exploration of the Hurd–Mori reaction for the formation of bicyclic 1,2,3-thiadiazoles, because they show how several interrelated constitutional elements of the pre-existing ring determine the reaction product in a way that could not have been predicted a priori. From the various examples presented, it can be concluded that an electron withdrawing (methyl ester or cyano) group on the existing ring strongly increases the conversion efficiency to the fused thiadiazole product. This effect is observed even when the substituent is in a remote position relative to the reactive centers. While promoting product formation, such an exocyclic group directs ring closure away from itself, as does an acylated ring nitrogen. The latter was found to dictate the regioselectivity completely when the two moieties adopt competitive positions. We can infer from these results that the operative process leading to ring closure is very susceptible to steric demand, even to the point where a methoxycarbonyl group at nitrogen—positioned in the plane of the ring due to conjugation—dominates in steric repulsion over an angular methoxycarbonyl group at a tetrahedral carbon atom, allowing attack of the sulfur moiety from the opposite side.

We would like to emphasize that the current mechanistic rationale is still a hypothesis and requires additional refinement. However, the present contributions to obtaining a better understanding of the concept provide a good basis for predictions for the chemical behavior of novel reaction precursors.

While the overall yields are moderate, it should be pointed out that this facile route accomplishes to produce these five-membered and strained bicyclic systems from commercially available or readily prepared starting materials. In particular, when a one-pot protocol is used, the synthesis is short and exclusive regioselectivity is observed, even when the governing forces of this selectivity are opposed to each other.

4. Experimental

4.1. General

Solvents were dried and distilled prior to use. Flash column chromatography was performed on silica gel 60 (40–63 μm), obtained from Merck. Melting points were determined using a Kofler type Leica Galen III micro hot stage microscope and are uncorrected. NMR spectra were recorded on a Bruker AC 200 spectrometer and chemical shifts are reported in parts per million, using TMS as internal standard. Combustion analysis was carried out at the Microanalytic Laboratory, University of Vienna.

4.2. Compounds

*4.2.1. 1-tert-Butyl 3-methyl 5-thioxopyrrolidine-1,3-dicarboxylate **1**.* Methyl 5-thioxopyrrolidine-3-carboxylate (2.13 g, 13.4 mmol, 1.00 equiv), DMAP (1.63 g, 13.4 mmol, 1.00 equiv), and Et_3N (1.35 g, 13.4 mmol, 1.00 equiv) were combined with anhydrous CH_2Cl_2 (100 mL) and Boc_2O (2.92 g, 13.4 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) was added dropwise at −70 to −60 °C. The solution was stirred for 48 h, thereby warming it slowly to rt; then the solvent and Et_3N were removed in vacuo and the residue was redissolved in CH_2Cl_2. Silica gel (5 g) was added and the crude product was adsorbed by solvent evaporation. Purification via flash column chromatography (petrol ether/EtOAc, 5:1) afforded **1** (2.56 g, 9.87 mmol, 74%); mp 121–124 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.56 (s, 9H), 3.18–3.38 (m, 3H), 3.76 (s, 3H), 4.28 (d, J 6.9 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.9 (q), 37.4 (d), 50.8 (t), 52.5 (q), 55.0 (t), 84.4 (s), 149.8 (s), 165.1 (s), 172.0 (s), 203.9 (s).

Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 51.19; H, 6.67; N, 5.35.

4.2.2. 1-tert-Butyl 3-methyl 5-[2-(ethoxycarbonyl)hydrazono]pyrrolidine-1,3-dicarboxylate ***2***. Compound **1** (1.70 g, 6.55 mmol, 1.00 equiv) and ethyl hydrazinecarboxylate (0.68 g, 6.55 mmol, 1.00 equiv) were combined with anhydrous CH_2Cl_2 (25 mL) and refluxed for 21 h. Concentration in vacuo gave a viscous oil, to which sufficient EtOAc was added at elevated temperature to achieve complete dissolution. Storage at −35 °C for 48 h and filtration of the precipitate afforded **2** (2.11 g, 6.40 mmol, 98%); mp 123–125 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, *J* 7.1 Hz, 3H), 1.54 (s, 9H), 2.97–3.27 (m, 3H), 3.74 (s, 3H), 3.89 (dd, *J* 10.6 Hz, 6.9 Hz, 1H), 3.98 (dd, *J* 10.6 Hz, 8.0 Hz, 1H), 4.22 (q, *J* 7.0 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.4 (q), 28.0 (q), 29.9 (t), 36.9 (d), 49.8 (t), 52.4 (q), 61.6 (t), 82.2 (s), 145.0 (s), 156.0 (s), 172.0 (s); C5 gives no signal.

4.2.3. 4-tert-Butyl 6-methyl 4H-pyrrolo[2,3-d][1,2,3]thiadiazole-4,6-dicarboxylate ***3***. Compound **2** (0.35 g, 1.06 mmol, 1.00 equiv) dissolved in anhydrous CH_2Cl_2 was added dropwise over 1 h to a solution of $SOCl_2$ (0.58 mL, 7.4 mmol, 7.00 equiv) in CH_2Cl_2 at −10 to −5 °C and allowed to warm to rt while stirring overnight. The mixture was concentrated in vacuo and redissolved in CH_2Cl_2. Then Et_3N was added, concentration and redissolution were repeated and the solution was washed with H_2O, dried with Na_2SO_4, filtered, and the solvent removed; recrystallization from EtOAc afforded **3** (0.246 g, 0.87 mmol, 82%); mp (decomp.) 120–123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74 (s, 9H), 3.94 (s, 3H), 8.33 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.9 (q), 52.3 (q), 87.3 (s), 110.0 (s), 133.9 (s) and (d) isochronous, 146.3 (s), 158.4 (s), 162.2 (s). Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.64; H, 4.62; N, 14.83. Found: C, 46.83; H, 4.45; N, 14.89.

4.2.4. Methyl 4H-pyrrolo[2,3-d][1,2,3]thiadiazole-6-carboxylate ***4***. Compound **3** (0.20 g, 0.71 mmol, 1.00 equiv) and CF_3CO_2H (0.02 g, 25 mol%) were dissolved in anhydrous CH_2Cl_2 (15 mL) and refluxed for 5 h. Concentration in vacuo and recrystallization from EtOAc afforded **4** (0.125 g, 0.69 mmol, 98%); mp 218–220 (change in crystal morphology at 195 °C). All characterization data in accordance with Ref. 18.

4.2.5. Methyl 2-thioxopyrrolidine-1-carboxylate ***5***. Pyrrolidine-2-thione (10.0 g, 98.8 mmol, 1.00 equiv), DMAP (12.1 g, 98.8 mmol, 1.00 equiv), and Et_3N (10.0 g, 98.8 mmol, 1.00 equiv) were combined with anhydrous CH_2Cl_2 (200 mL) and methyl chloroformate (18.7 g, 197 mmol, 2.00 equiv) in CH_2Cl_2 was added dropwise at −70 to −60 °C. The solution was stirred for 12 h and thereby it warmed slowly to rt; then the solvent, Et_3N, and residual methyl chloroformate were evaporated in vacuo, DMAP and Et_3NHCl were removed via flash column chromatography (petrol ether/EtOAc, 1:1) and the crude product recrystallized from EtOAc to afford **5** (15.3 g, 96.1 mmol, 97%); mp 40–42 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02 (quin, *J* 7.5 Hz, 2H), 3.00 (t, *J* 7.8 Hz, 2H), 3.80 (s, 3H), 4.05 (t, *J* 7.2 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 19.8 (t), 48.3 (t), 53.1 (q), 53.2 (t), 151.7 (s), 207.6 (s).

4.2.6. Methyl 2-[2-(ethoxycarbonyl)hydrazono]pyrrolidine-1-carboxylate ***6***. Compound **5** (15.0 g, 94.2 mmol, 1.00 equiv) and ethyl hydrazinecarboxylate (9.8 g, 94.2 mmol, 1.00 equiv) were combined with anhydrous CH_2Cl_2 (80 mL) and stirred for 72 h at rt. Concentration in vacuo, redissolution in $CHCl_3$, storage at −35 °C for 48 h, and filtration of the precipitate afforded **6** (16.5 g, 89.1 mmol, 95%); mp 82–84 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, *J* 7.1 Hz, 3H), 2.00 (quin, *J* 7.5 Hz, 2H), 2.73 (t, *J* 7.8 Hz, 2H), 2.84 (br s, 1H), 3.78 (t, *J* 7.2 Hz, 2H), 3.82 (s, 3H), 4.22 (q, *J* 7.1 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.3 (q), 19.2 (t), 26.7 (t), 48.1 (t), 53.0 (q), 61.5 (t), 152.2 (s), 154.6 (s); C2 gives no signal.

4.2.7. Methyl 4H-pyrrolo[2,3-d][1,2,3]thiadiazole-4-carboxylate ***7***. Compound **6** (10.00 g, 54.0 mmol, 1.00 equiv), dissolved in anhydrous CH_2Cl_2 (50 mL), was added dropwise over 1 h to a solution of $SOCl_2$ (29.6 mL, 378 mmol, 7.00 equiv) in CH_2Cl_2 (150 mL) at −10 to −5 °C and allowed to warm to rt while stirring overnight. The mixture was concentrated in vacuo, redissolved in CH_2Cl_2, washed with satd aq $NaHCO_3$ and H_2O, dried with Na_2SO_4, filtered, and the solvent removed. Purification via flash column chromatography and recrystallization from DIPE afforded **7** (2.90 g, 15.8 mmol, 29%); mp 108–111 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.19 (s, 3H), 6.71 (d, *J* 3.7 Hz, 1H), 7.83 (d, *J* 3.7 Hz, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 54.9 (q), 102.7 (d), 130.6 (d), 136.2 (s), 149.1 (s), 158.4 (s).

4.2.8. 4H-Pyrrolo[2,3-d][1,2,3]thiadiazole ***8***. Compound **7** (0.50 g, 2.70 mmol, 1.00 equiv) was added to anhydrous MeOH (10 mL), combined with excess KOH (7.5 g) dissolved in MeOH, and the solution refluxed for 16 h. It was neutralized with CF_3CO_2H (15.3 g), concentrated, and dried in vacuo, then repeatedly heated in DIPE and filtered to extract the crude product from the inorganic residue. The filtrated fractions were combined and the solvent was evaporated to afford **8** (0.27 g, 2.16 mmol, 79%) by recrystallization from EtOAc; mp 87–88 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.59 (d, *J* 3.0 Hz, 1H), 7.68 (d, *J* 3.0 Hz, 1H), 8.63 (br s, 1H). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 98.6 (d), 130.8 (s), 131.8 (d), 161.6 (s).

4.2.9. 1-tert-Butyl 2-methyl 5-thioxopyrrolidine-1,2-dicarboxylate ***9***. Methyl 5-thioxopyrrolidine-2-carboxylate (4.41 g, 27.7 mmol, 1.00 equiv), DMAP (3.37 g, 27.7 mmol, 1.00 equiv), and Et_3N (2.80 g, 27.7 mmol, 1.00 equiv) were combined with anhydrous CH_2Cl_2 (200 mL); Boc_2O (6.04 g, 27.7 mmol, 1.00 equiv) in CH_2Cl_2 (80 mL) was added dropwise at −70 to −60 °C. The solution was stirred for 48 h, thereby warming it slowly to rt; then the solvent and Et_3N were removed in vacuo and the residue redissolved in CH_2Cl_2. Silica gel (10 g) was added and the crude product then adsorbed by solvent evaporation. Purification via flash column chromatography afforded **9** (5.61 g, 21.63 mmol, 78%); mp 114–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 2.02–2.54 (m, 2H), 3.03–3.18 (m, 2H), 3.81 (s, 3H), 4.95 (dd, *J* 9.5 Hz, 2.9 Hz, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.0 (t), 27.6 (q), 46.8 (t), 52.4 (s), 65.6 (d), 84.4 (s), 149.3 (s), 170.8 (s), 206.7 (s). Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 51.19; H, 6.55; N, 5.35.

4.2.10. 4-tert-Butyl 5-methyl 4H-pyrrolo[2,3-d][1,2,3]thiadiazole-4,5-dicarboxylate ***11***. Compound **9** (0.61 g, 2.35 mmol, 1.00 equiv), ethyl hydrazinecarboxylate (0.24 g, 2.35 mmol, 1.00 equiv), and anhydrous CH_2Cl_2 were combined and refluxed for 72 h (until H_2S ceased to evolve). The mixture was concentrated to dryness, redissolved in anhydrous CH_2Cl_2 and then added dropwise over 1 h to a solution of $SOCl_2$ (1.29 mL, 16.5 mmol, 7.00 equiv) in CH_2Cl_2 at −10 to −5 °C and allowed to warm to rt while stirring overnight. The mixture was concentrated in vacuo and redissolved in CH_2Cl_2. Then Et_3N was added, concentration, and redissolution were repeated and the solution was washed with H_2O, dried with Na_2SO_4, filtered, and the solvent removed; purification via flash column chromatography afforded **11** (0.351 g, 1.24 mmol, 53%); mp (decomp.) 105–108 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58 (s, 9H), 3.85 (s, 3H), 7.02 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.3 (q), 52.5 (q), 86.3 (s), 106.9 (d), 132.2 (s), 133.9 (s), 146.0 (s), 160.2 (s) and (d) isochronous. Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.64; H, 4.62; N, 14.83. Found: C, 46.55; H, 4.45; N, 14.77.

4.2.11. Methyl 4H-pyrrolo[2,3-d][1,2,3]thiadiazole-5-carboxylate ***12***. Compound **11** (0.20 g, 0.71 mmol, 1.00 equiv) and CF_3CO_2H (0.02 g,

25 mol %) were dissolved in anhydrous CH_2Cl_2 (10 mL) and refluxed for 5 h. Concentration in vacuo and recrystallization from EtOAc afforded **12** (0.112 g, 6.88 mmol, 97%); mp 186–188 °C (sublimes at 150–160 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.91 (s, 3H), 7.22 (d, *J* 1.9 Hz, 1H; becomes singlet on D–H exchange), 7.60 (br s, 1H). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 52.3 (q), 103.8 (d), 123.0 (s), 132.5 (s), 161.1 (s), 161.6 (s). Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.34; H, 2.75; N, 22.94. Found: C, 39.57; H, 2.70; N, 22.73.

*4.2.12. Dimethyl 4H-pyrrolo[3,4-d][1,2,3]thiadiazole-5,6(6H)-dicarboxylate **16**.* Compound **13** (5.11 g, 25.4 mmol, 1.00 equiv), tosylhydrazide (4.73 g, 25.4 mmol, 1.00 equiv), and anhydrous EtOH (50 mL) were combined and stirred for 16 h at rt. The mixture was concentrated to dryness, redissolved in anhydrous CH_2Cl_2 (50 mL) and then added dropwise to a solution of $SOCl_2$ (13.9 mL, 178 mmol, 7 equiv) in CH_2Cl_2 (300 mL) at −20 °C. Then it was stirred at −16 °C for 4 h and subsequently at rt for 5 h. The mixture was concentrated in vacuo, redissolved in CH_2Cl_2, repeatedly washed with satd aq $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. Purification via flash column chromatography with concomitant removal of byproduct **17** and recrystallization from EtOAc afforded **16** (3.77 g, 15.5 mmol, 61%); mp 87–88 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 and 3.86 (2s, Σ3H), 3.82 (s, 3H), 4.97–5.08 (m, 2H), 5.77 and 5.83 (2dd, *J* 3.0 Hz, *J* 3.2 Hz, Σ1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 46.6 and 46.9 (2t), 53.3 and 53.5 (2q), 60.8 and 60.9 (2d), 146.6 and 146.8 (2s), 154.2 and 154.9 (2s), 165.1 and 165.4 (2s), 167.3 and 167.5 (2s). Anal. Calcd for $C_8H_9N_3O_4S$: C, 39.50; H, 3.73; N, 17.27. Found: C, 39.80; H, 3.69; N, 17.29.

*4.2.13. Dimethyl 5H-pyrrolo[3,4-d][1,2,3]thiadiazole-5,6-dicarboxylate **17**.*[20] Compound **16** (2.03 g, 8.35 mmol, 1.00 equiv) and DDQ (1.89 g, 8.35 mmol, 1.00 equiv) were combined with 1,4-dioxane (25 mL) and refluxed for 40 h. The solvent was removed in vacuo and the residue redissolved in CH_2Cl_2; silica gel (3 g) was added to adsorb the crude product by solvent evaporation. Purification via flash column chromatography afforded **17** (1.85 g, 7.67 mmol, 92%); mp 116–118 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.11 (s, 3H), 7.58 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 52.3 (q), 55.4 (q), 110.1 (d), 128.0 (s), 129.3 (s), 133.2 (s), 155.2 (s), 159.3 (s). Anal. Calcd for $C_8H_7N_3O_4S$: C, 39.83; H, 2.92; N, 17.42. Found: C, 39.89; H, 3.00; N, 17.39.

*4.2.14. Methyl 5H-pyrrolo[3,4-d][1,2,3]thiadiazole-6-carboxylate **18**.* Compound **17** (0.50 g, 2.07 mmol, 1.00 equiv) was suspended in aq HCl (37.5 g, 8 mol L^{-1}) and refluxed for 8 days. The mixture was concentrated in vacuo and residual H_2O removed by repeated azeotropic distillation with $CHCl_3$. The crystalline intermediate was dissolved in HCl/satd anhydrous MeOH (10 mL) at 25 °C and stirred for 5 h, then more HCl/satd MeOH (5 mL) was added and the solution refluxed for 2 h. Solvent evaporation and recrystallization from EtOAc afforded **18** (0.158 g, 0.86 mmol, 42%); mp (decomp.) 197–201 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.86 (s, 3H), 7.38 (br s, 1H), 8.37 (d, *J* 3.7 Hz, 1H; becomes singlet on D–H exchange). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 51.9 (q), 108.3 (s), 115.1 (d), 129.8 (s), 159.4 (s), 159.6 (s). Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.34; H, 2.75; N, 22.94. Found: C, 39.60; H, 2.79; N, 22.71.

*4.2.15. Methyl 5,6-dihydro-4H-cyclopenta[d][1,2,3]thiadiazole-5-carboxylate **25**.* Compound **24** (1.40 g, 9.85 mmol, 1.00 equiv), tosylhydrazide (1.83 g, 9.85 mmol, 1.00 equiv), and anhydrous EtOH (50 mL) were combined and stirred overnight at rt. The mixture was concentrated to dryness, suspended in anhydrous CH_2Cl_2 (50 mL), then added dropwise to a solution of $SOCl_2$ (5.4 mL, 69 mmol, 7.00 equiv) in CH_2Cl_2 (150 mL) at −10 °C and allowed to warm to rt over 4 h. The mixture was concentrated in vacuo and redissolved in CH_2Cl_2. Then excess Et_3N was added and the solution repeatedly washed with brine, dried with Na_2SO_4, filtered, and the solvent removed. Purification via flash column chromatography and *Kugelrohr* distillation afforded **25** (0.827 g, 4.49 mmol, 46%); bp 125–130 °C/0.01 mbar. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.36–3.54 (m, 4H), 3.78 (s, 3H), 3.93–4.15 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 28.1 (t), 28.7 (t), 48.0 (d), 51.9 (q), 152.9 (s), 169.1 (s), 173.2 (s). Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.74; H, 4.33; N, 15.07.

*4.2.16. 5,6-Dihydro-4H-cyclopenta[d][1,2,3]thiadiazole-5-carbonitrile **27**.* Compound **26** (0.66 g, 6.00 mmol, 1.00 equiv), tosylhydrazide (1.13 g, 6.00 mmol, 1.00 equiv), and anhydrous CH_2Cl_2 (30 mL) were combined and stirred overnight at rt (a white precipitate could be observed after 3 h). The mixture was concentrated to dryness, redissolved in anhydrous CH_2Cl_2 (10 mL), then added dropwise to a solution of $SOCl_2$ (3.3 mL, 42 mmol, 7.00 equiv) in CH_2Cl_2 (10 mL) at −10 °C and allowed to warm to rt over 5 h. The mixture was concentrated in vacuo and redissolved in CH_2Cl_2. Then excess Et_3N was added and the solution repeatedly washed with brine, dried with Na_2SO_4, and filtered. Silica gel (2 g) was added and the crude product adsorbed by solvent evaporation. Purification via flash column chromatography and *Kugelrohr* distillation afforded **27** (0.406 g, 2.69 mmol, 45%); bp 110–115 °C/0.01 mbar. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.33–3.75 (m, 4H), 3.97–4.15 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 29.9 (t), 30.7 (t), 32.4 (d), 120.3 (s), 151.9 (s), 168.1 (s). Anal. Calcd for $C_6H_5N_3S$: C, 47.67; H, 3.33; N, 27.79. Found: C, 47.89; H, 3.44; N, 27.85.

*4.2.17. Methyl 5,6-dihydro-4H-cyclopenta[d][1,2,3]thiadiazole-4-carboxylate **31**.* Compound **30** (6.90 g, 48.5 mmol, 1.00 equiv), tosylhydrazide (9.03 g, 48.5 mmol, 1.00 equiv), and anhydrous EtOH (100 mL) were combined and stirred for 16 h at rt. The mixture was concentrated to dryness, suspended in anhydrous CH_2Cl_2 (100 mL), then added dropwise to a solution of $SOCl_2$ (26.7 mL, 340 mmol, 7.00 equiv) in CH_2Cl_2 (150 mL) at −10 °C and stirred at 0 °C for 64 h. The mixture was concentrated in vacuo and redissolved in CH_2Cl_2. Then, excess Et_3N was added and the solution was repeatedly washed with H_2O, dried with Na_2SO_4, filtered, and the solvent removed. Purification via flash column chromatography and *Kugelrohr* distillation afforded **31** (5.04 g, 27.4 mmol, 56%); bp 125–130 °C/0.01 mbar. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.97–3.32 (m, 4H), 3.76 (s, 3H), 4.27–4.39 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.5 (t), 34.8 (t), 42.2 (d), 51.9 (q), 156.9 (s), 168.1 (s), 171.6 (s). Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.94; H, 4.28; N, 15.35.

*4.2.18. 4-tert-Butyl 6-methyl 4H-pyrrolo[3,2-d][1,2,3]thiadiazole-4,6-dicarboxylate **33**.* Compound **32** (6.75 g, 27.9 mmol, 1.00 equiv), tosylhydrazide (5.12 g, 27.9 mmol, 1.00 equiv), and anhydrous EtOH (100 mL) were combined and stirred for 16 h at rt. The mixture was concentrated to dryness, suspended in anhydrous CH_2Cl_2 (70 mL) and then added dropwise to a solution of $SOCl_2$ (15.3 mL, 195 mmol, 7.00 equiv) in CH_2Cl_2 (150 mL) at −20 °C. Then, it was stirred at −16 °C for 4 h and subsequently at rt for 5 h. The mixture was concentrated in vacuo, redissolved in CH_2Cl_2, repeatedly washed with satd aq $NaHCO_3$, dried with Na_2SO_4, filtered, and the solvent removed. Purification via flash column chromatography and recrystallization from EtOAc afforded **33** (2.15 g, 7.54 mmol, 27%); mp 129–131 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (s, 9H), 4.01 (s, 3H), 8.21 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.6 (q), 52.1 (q), 87.9 (s), 110.6 (s), 133.2 (d), 141.2 (s), 146.3 (s), 155.7 (s), 161.9 (s). Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.64; H, 4.63; N, 14.83. Found: C, 46.91; H, 4.51; N, 14.80.

*4.2.19. Methyl 4H-pyrrolo[3,2-d][1,2,3]thiadiazole-6-carboxylate **34**.* Compound **33** (0.70 g, 2.47 mmol, 1.00 equiv) and CF_3CO_2H (0.07 g, 25 mol %) were dissolved in anhydrous CH_2Cl_2 (20 mL) and refluxed for 5 h. Concentration in vacuo and recrystallization from EtOAc afforded **34** (0.435 g, 2.37 mmol, 96%); mp (decomp.) 195–205 °C. ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-d_6, 3:20): δ 3.85 (s, 3H), 8.10 (s, 1H), 8.91 (br s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$/DMSO-d_6, 3:20): δ 51.3 (q), 105.0 (s), 136.4 (d), 141.8 (s), 156.0 (s), 162.5 (s).

Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.34; H, 2.75; N, 22.94. Found: C, 39.58; H, 2.77; N, 22.69.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.017. These data include MOL file and InChiKeys of the most important compounds described in this article.

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