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ACCEPTED MANUSCRIPT

Nitrogen-Bridged Heterocycles via Cycloaddition of Non-Classical Heterocyclic-fused-[*c*]thiazoles

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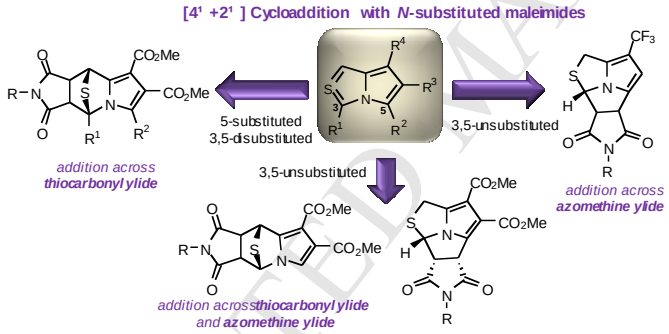
The [4π+2π] cycloaddition of non-classical heterocyclic-fused-[*c*]thiazoles was explored allowing the synthesis of a range of new nitrogen-bridged bi-, tri- and tetracyclic heterocyclic compounds namely, pyrazolo[1,5-*a*]pyridines, thiazolo[2,3,4-*cd*]pyrrolizines and indolizines. For the first time, one non-classical pyrrolo[1,2-*c*]thiazole was isolated and its structure determined by X-ray crystallography.

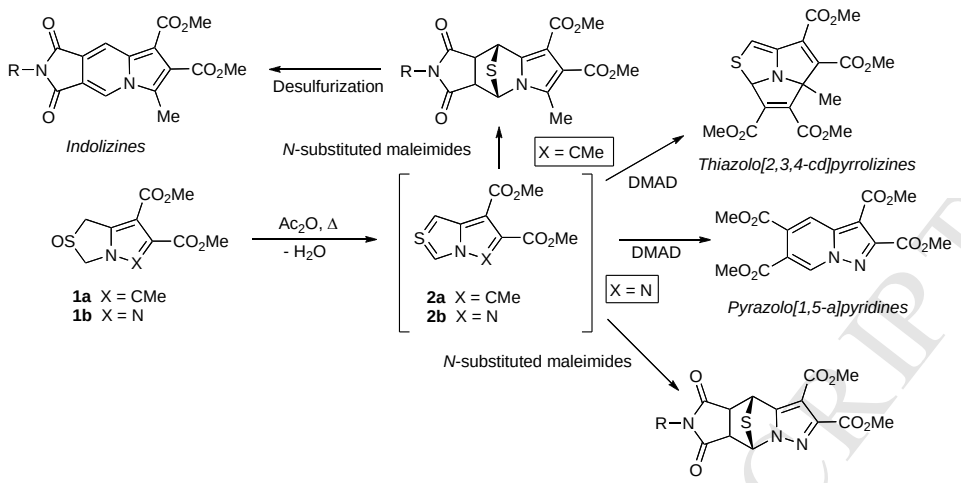


1. Introduction

Heteropentalene mesomeric betaines are bicyclic 10π-electron heterocycles isoconjugate with the pentalenyl dianion which cannot be represented by classic covalent Kekulé structures. They can only be represented by dipolar structures or by structures involving tetravalent sulphur atoms. Their interesting electronic structure makes them of interest from both theoretical and synthetic point of view. These non-classical heteropentalenes are versatile substrates in cycloaddition reactions for the construction of a variety of fused heterocycles.[1]

The non-classical heteropentalenes **2**, containing a tetravalent sulphur atom, can be generated *in situ* via Pummerer-type dehydration of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **1a** and 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole **1b**, respectively (Scheme 1). These transient heterocyclic-fused-[*c*]thiazole systems **2** participate in [4π+2π] cycloadditions to give fused heterocycles.[2,3] Heteropentalene **2a** reacts as thiocarbonyl ylide in the reaction with *N*-substituted maleimides, whereas with acetylene dicarboxylate intermediate **2a** acts as an azomethine ylide. Heteropentalene **2b** reacts with both types of dipolarophiles,

giving products resulting from the addition across the thiocarbonyl ylide moiety.



Scheme 1. [4π+2π] cycloadditions of non-classical heterocyclic-fused-[*c*]thiazoles **2**.

This chemistry allows the synthesis of interesting nitrogen-bridged bicyclic and tricyclic heterocyclic compounds namely, pyrazolo[1,5-*a*]pyridines, thiazolo[2,3,4-*cd*]pyrrolizines and indolizines. In fact, indolizine is an important structural unit commonly found in naturally occurring alkaloids and biologically active molecules, thus representing an important class of heterocycles in drug discovery. For instance, substituted indolizines have shown antioxidant[4] and antimycobacterial properties,[5] while some derivatives are slow-channel calcium antagonists[6] and others show inhibitory activity of secretory phospholipases A_2,[7] phosphatase[8] and 15-lipoxygenase.[9] On the other hand, indolizine-glyoxylamides showed cytotoxicity against multidrug resistant cancer cell lines.[10] Pyrazolo[1,5-*a*]pyridines represent another important class of *N*-bridged heterocycles with recognized biological activity. Compounds incorporating a pyrazolo[1,5-*a*]pyridine core are highly selective dopamine D_3 and D_4 receptor agonists and antagonists used for the treatment of neurophathological disorders such as schizophrenia and Parkinson's disease.[11] Some derivatives were found to be selective adenosine A_1 receptor antagonists with potent diuretic[12] and herpetic activity.[13] More recently a 2,3-substituted pyrazolo[1,5-*a*]pyridine was identified as a promising p38 kinase inhibitor.[14]

In this context, the chemistry of non-classical heterocyclic-fused-[*c*]thiazoles was further explored aiming to access a range of new nitrogen-bridged bicyclic and tricyclic heterocyclic compounds.

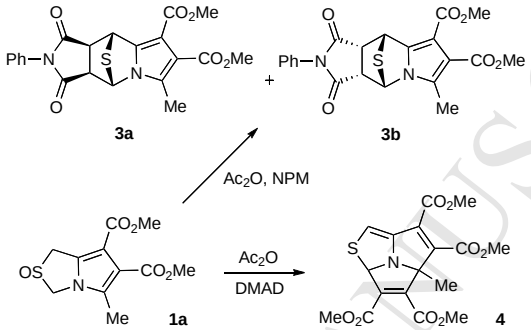
2. Results and Discussion

Initially, we looked again into cycloadditions of heteropentalene **2a** with *N*-phenylmaleimide (NPM) and dimethyl acetylene dicarboxylate (DMAD) reported by Kane and Storr (Table 1).[2,3] Pummerer-type dehydration of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **1a** in boiling acetic anhydride in the presence of NPM gave a mixture of the *exo*- and *endo*-cycloadducts via [4π+2π] cycloaddition across the thiocarbonyl ylide portion of heteropentalene **2a** as previously described[2,3] (Table 1). Carrying out the reaction for 4 h the *exo*-cycloadduct **3a** was isolated in 54% yield as the major product together with the synthesis of the

endo-cycloadduct **3b** in 8% yield (Table 1, Entry 1). Longer reaction time led to compound **3a** in low yield, indicating lack of stability of the cycloadducts to these reaction conditions (Table 1, Entry 2). Sealed tube thermolysis at 140 ºC for 4 h gave a good overall yield, the *exo*-cycloadduct **3a** being again the major product (Table 1, Entry 3). It was demonstrated that heteropentalene **2a** can also be generated under microwave irradiation (MW). The same pattern of reactivity was observed in the cycloaddition of **2a** with NPM carrying out the microwave irradiation with the temperature set to 140 ºC for 20 minutes, giving *exo*- and *endo*-cycloadducts **3** in 83% overall yield (Table 1, Entry 4).

Table 1

Cycloaddition of heteropentalene **2a** generated from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **1a**.

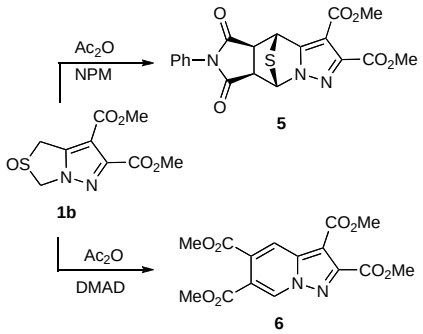


Entry	Dipolarophile	Reaction Conditions	Products (Yield)	
1	NPM	Reflux, 4 h	**3a** (54%)	**3b** (8%)
2	NPM	Reflux, 7 h	**3a** (16%)	---
3	NPM	Sealed tube, 140 ºC, 4 h	**3a** (58%)	**3b** (14%)
4	NPM	MW, 180 ºC, 20 min	**3a** (73%)	**3b** (10%)
5	DMAD	Reflux, 4 h	**4** (51%)	
6	DMAD	Sealed tube, 140 ºC, 4 h	**4** (35%)	
7	DMAD	MW, 180 ºC, 20 min	**4** (15%)	

The reaction of **1a** and DMAD in boiling acetic anhydride afforded the 1:1 adduct thiazolo[2,3,4-*cd*]pyrrolizine **4** in 51% yield via cycloaddition across the azomethine ylide portion of the non-classical heterocyclic-fused-[*c*]thiazole **2a** (Table 1, Entry 5). Under these reaction conditions a complex mixture was obtained but crystallisation from methanol gave compound **4** in pure form, as described in the literature.[2,3] Carrying out the thermolysis at 140 ºC in a sealed tube for 4 h the tricyclic heterocyclic compound **4** was obtained in moderate yield (35%) whereas under microwave irradiation at 180 ºC for 20 minutes the target molecule **4** could only be isolated in 15% yield (Table 1, Entries 6 and 7). Thus, conventional thermolysis are the best reaction conditions for the synthesis of heterocycle **4.**

Subsequently, dehydration of 2-oxo-pyrazolo[1,5-*c*]thiazole **1b** in the presence of NPM and DMAD was explored (Table 2). In both cases exclusive formation of cycloadducts resulting from the addition across the thiocarbonyl ylide moiety of the non-classical fused-[*c*]thiazole **2b** was observed, as described in the literature.[2,3] The cycloaddition of **2b** with *N*-phenylmaleimide carried out in boiling acetic anhydride for 4 h gave *exo*-adduct **5** selectively in 42% yield (Table 2, Entry 1). The yield for the synthesis of compound **5** could be improved to 76% by increasing the reaction time to 7 h (Table 2, Entry 2). The same compound could also be obtained in good yield under sealed tube thermolysis (Table 2, Entries 3 and 4). The microwave induced reaction of heteropentalene **2b** with NPM gave compound **5** in 54% yield (Table 2, Entry 5).

Table 2
Cycloaddition of heteropentalene **2b** generated from 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole **1b**.

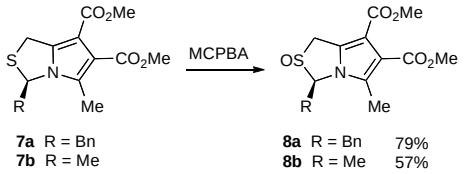


Entry	Dipolarophile	Reaction Conditions	Products (Yield)
1	NPM	Reflux, 4 h	**5** (42%)
2	NPM	Reflux, 7 h	**5** (76%)
3	NPM	Sealed tube, 140 ºC, 4 h	**5** (65%)
4	NPM	Sealed tube, 140 ºC, 7 h	**5** (71%)
5	NPM	MW, 180 ºC, 15 min	**5** (54%)
6	DMAD	Reflux, 4 h	**6** (26%)
7	DMAD	Reflux, 7 h	**6** (45%)
8	DMAD	Sealed tube, 140 ºC, 4 h	**6** (45%)
9	DMAD	MW, 160 ºC, 10 min	**6** (30%)
10	DMAD	MW, 180 ºC, 15 min	**6** (53%)

The non-classical thiazole **2b** reacts with DMAD giving pyrazolo[1,5-*a*]pyridine **6** resulting from the initial cycloaddition across the thiocarbonyl ylide portion of **2b** followed by spontaneous loss of sulphur. Carrying out the reaction in boiling acetic anhydride for 4 h compound **6** was obtained in only 26% yield but with a longer reaction time the yield could be improved to 45% (Table 2, Entries 6 and 7). The same yield was obtained carrying out the sealed tube thermolysis at 140 ºC for 4 h (Table 2, Entry 8). The dehydration of 2-oxo-pyrazolo[1,5-*c*]thiazole **1b** and the subsequent cycloaddition with DMAD was also achieved under microwave irradiation (Table 2, Entries 9 and 10). The best reaction conditions, microwave irradiation at 180 ºC for 15 minutes, afforded compound **6** in 53% yield.

Semi-empirical calculations reported by Storr *et al.* indicated that the cycloaddition of non-classical thiazoles **2** is dipole-HOMO controlled.[3] On the other hand the coefficients in the HOMO suggest that the addition across both thiocarbonyl ylide and azomethine or azomethine imine ylide portion of **2a** and **2b**, respectively, would be possible. However, exclusive formation of pyrazolo[1,5-*a*]pyridine adducts from **2b** in contrast with the synthesis of both types of adducts from **2a** can be explained considering the type of bonds being formed in each case. As mentioned by the authors, the calculation did not take into account this fact. In the case of **2a** both types of additions lead to two new carbon-carbon bonds whereas in the case of **2b** addition across the thiocarbonyl ylide moiety also leads to two new carbon-carbon bonds but the addition across the azomethine imine portion would lead to the formation of a carbon-carbon bond and to a less favourable carbon-nitrogen bond.

The work was extended to the synthesis and reactivity of new 3-benzyl and 2-oxo-3-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **8a** and **8b** in order to evaluate the scope of this approach to nitrogen-bridged heterocycles (Scheme 2, Tables 3 and 4). 1*H*,3*H*-Pyrrolo[1,2-*c*]thiazole **7a** and **7b** were prepared by a known procedure[15] and converted into the corresponding sulfoxides **8** by oxidation with MCPBA (Scheme 2).

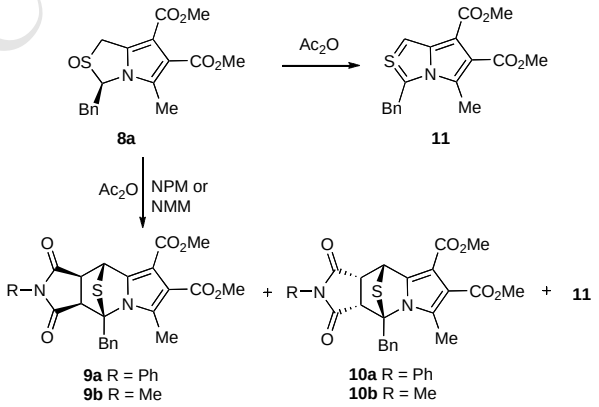


Scheme 2. Synthesis of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8**.

Interestingly, the oxidation of chiral 3-benzyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **7a** gave the corresponding sulfoxide **8a** as a 9:1 mixture of diastereoisomers which could be separated by flash chromatography to give the optically pure sulfoxides. The major isomer was isolated in 76% yield and the minor isomer was obtained in 3% yield. Thus, using an achiral oxidant a diastereoselective reaction was achieved, the stereochemistry of the sulfoxide being induced by the proximity of the chiral center at the α-position of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **7a**. Chiral sulfoxides are valuable for asymmetric synthesis due to the high asymmetric induction that can be exerted by the chiral sulfinyl group, making them interesting target molecules.[16]

Pummerer-type dehydration of 2-oxo-3-benzyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8a** in the presence of *N*-substituted maleimides was studied (Table 3). Under conventional heating for 4 h the cycloaddition reaction with *N*-phenylmaleimide gave a mixture of the *exo*- and *endo*-cycloadducts **9a** and **10a** in 22% and 20% yield, respectively (Table 3, Entry 1). Interestingly, from this reaction the non-classical thiazole **11** resulting from sulfoxide **8a** dehydration, was also isolated. The structure of heterocycle **11** was established by X-ray crystallography (Figure 1). This compound crystallized, in the monohydrated form, as yellow plates in the monoclinic system within *Cc* space group, showing a planar heterocyclic backbone. All distances and angles are within the expected values for similar compounds,[17] the benzyl substituent making an angle of 33.7º with the pyrrolo[1,2-*c*]thiazole. The carboxylate substituents on consecutive carbons of the pyrrole fragment, make an angle of 47.0º due to the high steric hindrance introduced.

Table 3
Generation and cycloaddition of heteropentalene **11**.



Entry	Dipolarophile	Reaction Conditions	Products (Yield)
1	NPM	Reflux, 4 h	**9a** (22%) **10a** (20%) **11** (23%)
2	NPM	MW, 160 ºC	**9a** (10%) **10a** (23%) **11** (36%)

		20 min			
3	NMM	Reflux, 4 h	**9b** (10%)	**10b** (39%)	**11** (21%)
4	NMM	Sealed tube 140 ºC, 4 h	---	**10b** (10%)	**11** (16%)
5	NMM	MW, 160 ºC 20 min	**9b** (6%)	**10b** (8%)	**11** (17%)
6	----	Reflux, 4 h		**11** (50%)	
7	----	MW, 160 ºC 25 min		**11** (33%)	

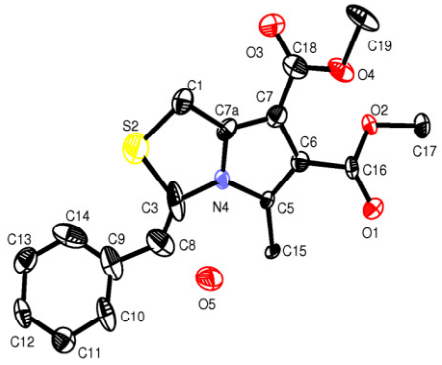


Figure 1. ORTEP-3 diagram of compound **11**, using 50% probability level ellipsoids. Hydrogen atoms have been omitted for clarity.

The *exo*/*endo* assignments of cycloadducts **9a** and **10a** were based on previously described ^{1}H NMR data of similar derivatives, characterized by a larger deshielding effect of the sulphur bridge on the imide α-protons of the *endo*-cycloadduct.[3,18] The structural assignment of compound **10a** was also supported by two-dimensional HSQC and NOESY spectra (400 MHz). In the NOESY spectrum sulphur bridge proton H-9 (5.28 ppm) shows connectivity with imide α-proton H-9a (3.98 ppm) and aliphatic benzyl protons (3.78 and 4.38 ppm) are correlated with imide α- proton H-3a (3.92 ppm).

Under microwave irradiation at 160 ºC for 20 minutes compounds **9a**, **10a** and **11** were obtained, the heteropentalene **11** being the major product (Table 3, Entry 2). The reaction of 2-oxo-3-benzyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8a** with *N*-methylmaleimide in boiling acetic anhydride for 4 h gave the expected 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[3,4-*f*]indolizines **9b** and **10b** together with the formation of heteropentalene **11** in 70% overall yield (Table 3, Entry 3). From the sealed tube thermolysis only *endo*-cycloadduct **10b** and compound **11** could be isolated in 10% and 16% yield, respectively (Table 3, Entry 4). The microwave induced reaction of sulfoxide **8a** in the presence of NMM gave compounds **9b**, **10b** and **11** in low overall yield (Table 3, Entry 5).

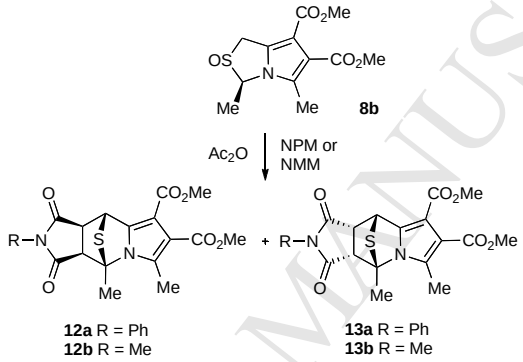
In the absence of a dipolarophile the dehydration of 2-oxo-3-benzyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8a** in boiling acetic anhydride for 4 h gave the non-classical heterocyclic-fused-[*c*]thiazole **11** in 50% yield whereas from the microwave induced dehydration compound **11** was isolated in lower yield (Table 3, Entries 6 and 7). However, attempts to carry out the reaction of non-classical heteropentalene **11** with NPM under conventional heating or under microwave irradiation only led to complex mixtures.

Although these new disubstituted heteropentalenes showed the expected reactivity for the [4π+2π] cycloaddition with maleimides, no reaction was observed with acetylene dicarboxylate.

The chemical behaviour of 2-oxo-3-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8b** under thermolysis in

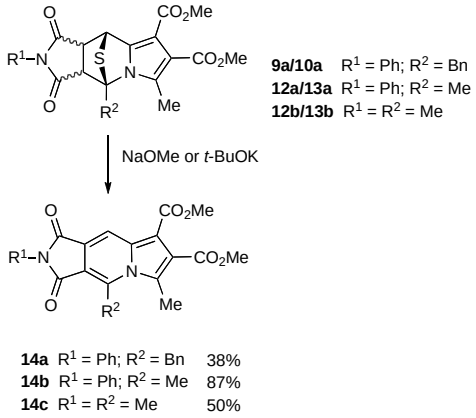
acetic anhydride in the presence of dipolarophiles was similar to the one observed for sulfoxide **8a**. In fact, [4π+2π] cycloadducts were obtained from the reaction with maleimides but no reaction was observed with acetylene dicarboxylate (Table 4). However, in this case the heteropentalene generated *in situ* from compound **8b** could not be isolated. The reaction of sulfoxide **8b** with NPM in boiling acetic anhydride for 4 h gave *exo*-cycloadduct **12a** and *endo*-cycloadduct **13a** in 39% and 15% yield, respectively (Table 4, Entry 1). Carrying out the reaction in a sealed tube at 140 ºC for 4 h compound **12a** was obtained in 36% yield and only traces of compound **13a** could be detected (Table 4, Entry 2). Under microwave irradiation compound **12a** was isolated in 20% yield (Table 4, Entry 3). The reaction of sulfoxide **8a** with *N*-methylmaleimide in boiling acetic anhydride or under sealed tube thermolysis gave the expected *endo*- and *exo*-cycloadducts **12b** and **13b** (Table 4, Entries 4 and 5).

Table 4
Cycloaddition of the heteropentalene generated from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **8b**.



Entry	Dipolarophile	Reaction Conditions	Products (Yield)	
1	NPM	Reflux, 4 h	**12a** (39%)	**13a** (15%)
2	NPM	Sealed tube, 140 ºC, 4 h	**12a** (36%)	**13a** trace
3	NPM	MW, 140 ºC, 20 min	**12a** (20%)	**13a** trace
4	NMM	Reflux, 4 h	**12b** (9%)	**13b** (23%)
5	NMM	Sealed tube, 140 ºC, 4 h	**12b** (20%)	**13b** (19%)

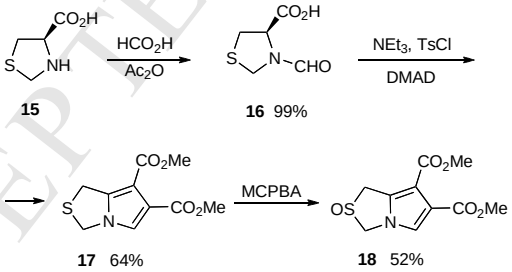
The mixture of *exo*- and *endo*-cycloadducts **9a**/**10a** and **12**/**13** underwent elimination of hydrogen sulfide on treatment with sodium methoxide or potassium *tert*-butoxide to afford indolizines **14** (Scheme 3). Attempts to promote the elimination of hydrogen sulfide with sodium methoxide from adducts **9b**/**10b** was not successful and led only to the recovery of the staring material. On the other hand, reaction with potassium *tert*-butoxide led to a complex mixture.



Scheme 3. Desulfirization of 4,9-epithio-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[3,4-f]indolizines.

The heteropentalenes derived from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles studied so far were 5-substituted heteropentalene **2a** or 3,5-substituted heteropentalenes (compound **11** and the heteropentalene derived from **8b**). Only the non-classical thiazole **2a** reacted as thiocarbonyl ylide in the reaction with *N*-substituted maleimides and as an azomethine ylide with acetylene dicarboxylate. Therefore, considering that steric effects may play a role in the observed reactivity, we decided to prepare and explore the reactivity of new 3,5-unsubstituted heteropentalenes.

3,5-Unsubstituted-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole sulfoxide **18** was prepared as outlined in Scheme 4. Formylation of thiazolidine **15** in high yield was achieved by the reaction with formic acid and acetic anhydride following a known procedure.[19] Treatment of the *N*-formylthiazolidine **16** with triethylamine and tosyl chloride in the presence of dimethyl acetylenedicarboxylate afforded pyrrolo[1,2-*c*]thiazole **17** in 64% yield. The oxidation of **17** with MCPBA afforded sulfoxide **18** in 52% yield.

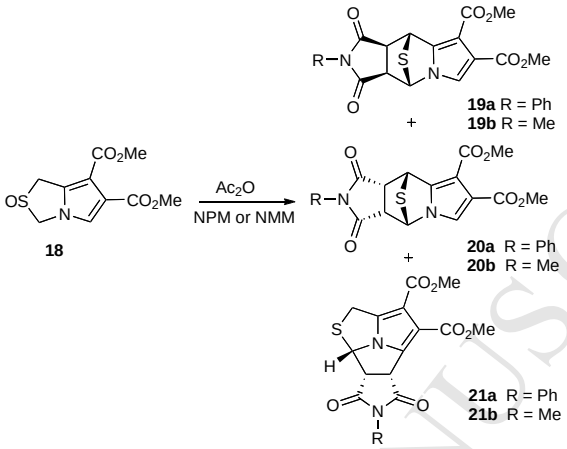


Scheme 4. Synthesis of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18**.

Dehydration of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18** led to the target 3,5-unsubstituted heteropentalene which was trapped with maleimides leading to products resulting from both additions across the thiocarbonyl ylide (compounds **19** and **20**) and azomethine ylide moieties (compound **21**) (Table 5). Carrying out the reaction of sulfoxide **18** in boiling acetic anhydride in the presence of NPM for 4 h cycloadducts **19a** (33%) and **21a** (18%) were obtained (Table 5, Entry 1) whereas the sealed tube thermolysis gave compounds **19a**, **20a** and **21a** in 47% overall yield (Table 5, Entry 2). The microwave induced reaction allowed the synthesis of the products resulting from the cycloaddition across the thiocarbonyl ylide portion of the *in situ* generated heteropentalene, the *exo*-cycloadduct **19a** in 55% yield and the *endo*-cycloadduct **20a** in 13% yield (Table 5, Entry 3). The dehydration of 2-oxo-1*H*,3*H*-

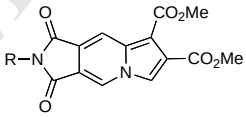
pyrrolo[1,2-*c*]thiazole **18** was also carried out in the pesence of NMM under different reaction conditions (Table 5, Entries 4-6). In all cases **19b**, **20b** and **21b** were obtained. Thus, for the first time a pyrrolo[1,2-*c*]thiazole heteropentalene reacted with *N*-substituted maleimides not only as a thiocarbonyl ylide but also as an azomethine ylide.

Table 5
Cycloaddition of the heteropentalene generated from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18**.



Entry	Dipolarophile	Reaction Conditions	Products (Yield)		
1	NPM	Reflux, 4 h	**19a** (33%)	---	**21a** (18%)
2	NPM	Sealed tube 140 ºC, 4 h	**19a** (28%)	**20a** (7%)	**21a** (12%)
3	NPM	MW, 180 ºC 20 min	**19a** (55%)	**20a** (13%)	---
4	NMM	Reflux, 4 h	**19b** (20%)	**20b** (9%)	**21b** (27%)
5	NMM	Sealed tube 140 ºC, 4 h	**19b** (19%)	**20b** (2%)	**21b** (16%)
6	NMM	MW, 180 ºC 20 min	**19b** (19%)	**20b** (8%)	**21b** (26%)

The mixture of *exo*- and *endo*-cycloadducts **19**/**20** underwent elimination of hydrogen sulfide on treatment with potassium *tert*-butoxide to afford indolizines **22**.



22a R = Ph 35%
22b R = Me 38%

The work was extended to a new non-classical thiazole derived from 3,5-unsubstituted-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole sulfoxide **24** (Table 6). Pyrrolo[1,2-*c*]thiazole **23** bearing only one trifluoromethyl group at C-7 was converted into the corresponding sulfoxide **24** by catalytic oxidation. By adjustment of an experimental procedure described in the literature for the synthesis of 2,2-dioxo-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole[20] a 92:8 mixture of sulfoxide **24** and the corresponding sulfone was obtained as a solid (using 2.4 equiv. of hydrogen peroxide). The solid was washed with diethyl ether giving sulfoxide **24** in pure form in 90% yield, without the need for further purification.

Dehydration of **24** in the presence of NPM led to a mixture of the *exo*- and *endo*-cycloadducts **25** (R = Ph). Sigmatropic H shift of these cycloadducts afforded the final products **26a** and **27a** in moderate yield

either in boiling acetic anhydride or under sealed tube thermolysis (Table 6, Entries 1-3). However, under microwave irradiation only traces of these products could be detected (Table 6, Entry 4). The structure of heterocycle **27a** was determined by X-ray crystallography (Figure 2). This compound crystallized as colourless prisms in the triclinic system within *P*-1 space group, as a racemic mixture. All distances and angles are within the expected values for similar compounds.[17] The compound displays an *endo* configuration, which is attested not only by the torsion angles around C4a-C4b and C7a-C7b (see Supplementary Information), but also from the angles between planes [C4b-C5-N6-C7-C7a] and [C4a-C4b-C7b-C7a-N8]; [C4b-C5-N6-C7-C7a] and [C2a-C3-C4-C4a-N8], and [C4a-C4b-C7b- C7a-N8] and [C2a-C3-C4-C4a-N8], respectively 64.5, 24.4 and 87.8º. The thiazolemoiety adopts an evelope conformation characterized by a value of 31.4º for the *hinge angle* that represents the bending at a line defined by atoms C2 and C7b.

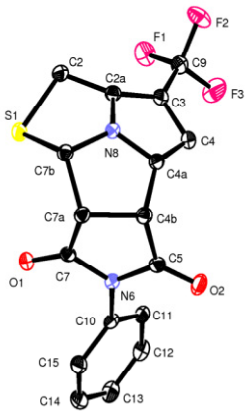
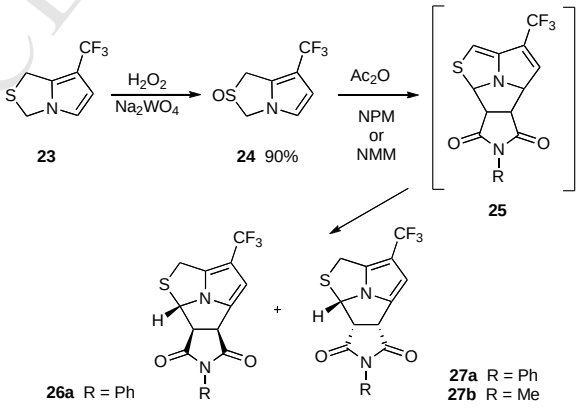


Figure 2. ORTEP-3 diagram of 5,7(4b*H*,6*H*)-dioxo-6-phenyl-3-(trifluoromethyl)-7a,7b-dihydro-2*H*-pyrrolo[3',4':5,6]thiazolo[2,3,4-*cd*]pyrrolizine **27a**, using 50% probability level ellipsoids. Hydrogen atoms have been omitted for clarity.

Table 6
Cycloaddition of the heteropentalene generated from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **24**.



Entry	Dipolarophile	Reaction Conditions	Products (Yield)	
1	NPM	Reflux, 4 h	**26a** (8%)	**27a** (13%)
2	NPM	Reflux, 7 h	**26a** (11%)	**27a** (30%)
3	NPM	Sealed tube, 140 ºC, 7 h	**26a** (10%)	**27a** (26%)
4	NPM	MW, 140 ºC, 20 min	**26a** trace	**27a** trace

5	NMM	Reflux, 7 h	---	**27b** (50%)
6	NMM	Sealed tube, 140 ºC, 7 h	---	**27b** (63%)

The dehydration of sulfoxide **24** in the presence of *N*-methylmeleimide was also explored, which led to the exclusive formation of the *endo*-cycloadduct **27b** (Scheme 10). Carrying out the reaction in boiling acetic anhydride for 7 h compound **27b** was obtained in 50% yield (Table 6, Entry 5). The sealed tube thermolysis allowed the isolation of the same product in 60 % yield (Table 6, Entry 6).

We could conclude that the heteropentalene derived from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **24** participates in [4π+2π] cycloadditions with *N*-substituted maleimides, but only as an azomethine ylide. Thus, steric and electronic factors must be considered in order to rationalize the observed selectivity.

3. Conclusions

The [4π+2π] cycloaddition of non-classical heterocyclic-fused-[*c*]thiazoles generated by dehydration of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles and 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazoles has been investigated giving access to new nitrogen-bridged bi-, tri- and tetracyclic heterocyclic compounds.

The reported results allowed for the definition of a reactivity pattern of this type of heteropentalenes towards *N*-substituted maleimides. The cycloaddition of the heteropentalene formed by dehydration of 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole-6,7-dicarboxylate leads to products resulting from the exclusive addition across the thiocarbonyl ylide moiety. 5-Substituted and 3,5-substituted heteropentalenes derived from 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates also react with *N*-substituted maleimides as thiocarbonyl ylide exclusively whereas the cycloaddition of the 3,5-unsubstituted derivative led to cycloadducts resulting from both the addition across the thiocarbonyl and azomethine ylide moieties. Interestingly, the non-classical heterocyclic-fused-[*c*]thiazole formed by dehydration of the 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole bearing only one trifluoromethyl group at C-7 reacted with *N*-substituted maleimides selectively as an azomethine ylide. Therefore, both steric and electronic factors must be considered in order to rationalize the observed selectivity.

For the first time, one non-classical pyrrolo[1,2-*c*]thiazole was isolated and its stucture determined by X-ray crystallography.

4. Experimental

4.1. General Methods.

^{1}H NMR spectra were recorded on an instrument operating at 300 or at 400 MHz. ^{13}C NMR spectra were recorded on an instrument operating at 100 MHz. Chemical shifts are expressed in parts per million related to internal TMS, and coupling constants (*J*) are in Hz. IR spectra were recorded on a Nicolet 6700 FTIR spectrometer. Mass spectra were recorded under electron impact (EI) or electrospray ionization (ESI). HRMS spectra were recorded on a Finnigan MAT95 S instrument. Melting points were determined

in open glass capillary with an Electrothermal melting point apparatus and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System, Discover S-Class.

1,3-Thiazolidine-4-carboxylic acid **15**,[3] 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **7**[19] and **23**[20], 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **1a**[3] and 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole **1b**[3] were prepared as described in the literature.

4.2. Specific chemical procedures.

*4.2.1. N-Formylthiazolidine-4-carboxylic acid (**16**). 1,3-Thiazolidine-4-carboxylic acid **15** (6.85 g, 51.5* mmol) was added to formic acid (53.0 mL), the temperature of the reaction medium being kept below 25 ºC. Acetic anhydride (35.0 mL) was added dropwise to the solution while maintaining the temperature between 10 and 18 ºC. After stirring for 20 h at a temperature of the order of 20 ºC, the solvent was evaporated off. The compound was obtained as a colourless oil (99%). IR (film) 2934, 1736, 1665, 1384, 1216 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *Major isomer:* δ 3.29-3.38 (m, 2H), 4.63 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 8.8 Hz, 1H), 5.09 (approx. t, J = 5.6 and 6.0 Hz, 1H), 7.64 (bs, 1H, O*H*), 8.35 (s, 1H, C*H*O); *Minor isomer:* δ 3.29-3.38 (m, 1H), 3.45 (dd, J = 1.6 and 11.6 Hz, 1H), 4.45 (d, J = 9.6 Hz, 1H), 4.76 (d, J = 9.6 Hz, 1H), 4.83-4.84 (m, 1H), 7.64 (bs, 1H, O*H*), 8.34 (s, 1H, C*H*O). MS (EI) *m/z* 161 (M^+, 17%), 116 (26), 89 (100). HRMS (EI-TOF) *m/z* 161.0151 (M^+, $C_5H_7NO_3S$ requires161.0147).

*4.2.2. Dimethyl 1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**17**).* Triethylamine (5.2 mL, 37.7 mmol) was added to a suspension of *N*-formylthiazolidine-4-carboxylic acid **16** (5.52 g, 34.3 mmol) in dry dichloromethane (15.0 mL). This solution was added dropwise to a mixture of tosyl chloride (7.34 g, 37.7 mmol) in dichloromethane (15.0 mL) at 40 ºC. Dimethyl acetylene dicarboxylate (4.7 mL, 38.4 mmol) was then added quickly followed by triethylamine (10.4 mL, 75.4 mmol). The reaction mixture was maintained refluxing for 3 h. After cooling to room temperature water was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane and the organic extracts are combined, dried over anhydrous sodium sulfate and the solvent evaporated off. Purification by flash chromatography [hexane- ethyl acetate (1:1), hexane-ethyl acetate (1:2), then ethyl acetate] gave **17** as a white solid (64%). mp 101-103 ºC (from ethylactetate/hexane). IR (KBr) 1728, 1708, 1433, 1285, 1130, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.83 (s, 3H), 4.27 (s, 2H), 5.04 (s, 2H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 49.1, 51.5, 51.6, 107.8, 120.5, 121.6, 142.8, 163.6, 163.7. MS (EI) *m/z* 241 (M^+, 30%), 209 (100), 164 (59), 151 (46), 134 (25), 123 (36). HRMS (EI-TOF) *m/z* 241.0412 (M^+, $C_{10}H_{11}NO_4S$ requires 241.0409).

*4.2.3. 2-Oxo-7-trifluoromethyl-1H,3H-pyrrolo[1,2-c]thiazole (**24**).* A 25 mL flask with a solution of 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **23** (4.03 mmol) in ethyl acetate (12 mL) was charge with $Na_2WO_4.H_2O$ (0.05 M in water, 12 μL, 0.6 μmol), $C_6H_5PO_3H_2$ (0.05 M in water, 12 μL, 0.6 μmol), $CH_3N[(CH_2)_7CH_3]Cl$ (0.05 M in methanol, 12 μL, 0.6 μmol) and 35% H_2O_2 (4.84 mmol). This mixture was vigorously stirred at 35-40 ºC. After 3 hours, a new load of catalyst was added and stirred overnight

at 35-40 ºC. The reaction mixture was washed with 10 % (w/v) aqueous sodium bisulfite and the aqueous phase was extracted with ethyl acetate. The organic phase was and then dried over anhydrous $MgSO_4$ and the solvent evaporated off. The crude product of the reaction was washed with ethyl ether giving compound **24** as a white solid in 90% yield. mp 101-102 ºC. IR (KBr) 1597, 1486, 1380, 1266, 1161, 1108, 1084, 1031, 979 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 16.4 Hz, 1H), 4.34 (dd, J = 1.0 and 16.4 Hz, 1H), 4.87 (d, J = 11.6 Hz, 1H), 5.06 (d, J = 11.6 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.6, 69.2, 110.3 (q, $J_{C\text{-}CF3}$ = 37.4 Hz), 111.9 (q, $J_{C\text{-}C\text{-}CF3}$ = 2.8 Hz), 117.4, 123.4 (q, $J_{C\text{-}F3}$ = 264.4 Hz), 129.3 (q, $J_{C\text{-}C\text{-}CF3}$ = 4.1 Hz). MS (EI) *m/z* 209 (M^+, 54%), 161 (100), 142 (15), 92 (14). HRMS (EI-TOF) *m/z* 209.0127 (M^+, $C_7H_6NOF_3S$ requires 209.0122).

4.3. General procedure for the synthesis of 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates.

To a stirred ice-cold solution of the appropriate dimethyl pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (13.0 mmol) in dry dichloromethane (70 mL) was added portionwise 3-chloroperoxybenzoic acid (13.0 mmol) under N_2 atmosphere. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1 h, the reaction mixture was washed twice with 10 % (w/v) aqueous sodium bisulfite solution (2 x 100 mL) and twice with 10 % (w/v) aqueous sodium bicarbonate solution (2 x 100 mL). The organic fraction was then dried over anhydrous sodium sulphate and the solvent evaporated off. The crude product was purified by flash chromatography [hexane-ethyl acetate].

*4.3.1. Dimethyl 2-oxo-3-benzyl-5-methyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**8a**).* Compound **8a** was obtained as a mixture of diastereoisomers which was separated by flash chromatography [hexane-ethyl acetate (1:2), ethyl acetate, then ethyl acetate-methanol (9:1)]. Major isomer was obtained as a white solid in 76% yield; mp 113-115 ºC (from ethyl ether). IR (KBr) 1729, 1684, 1644, 1558, 1451, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.20 (dd, J = 5.2 and 14.4 Hz, 1H, CH_2Ph), 3.28 (dd, J = 4.8 and 14.4 Hz, 1H, CH_2Ph), 3.36 (d, J = 17.4 Hz, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 3.99 (d, J = 14.4 Hz, 1H), 5.23 (approx. t, J = 5.2 Hz, 1H, C*H*Bn), 6.88-6.89 (m, 2H, ArH), 7.25-7.31 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 37.3, 51.4, 51.6, 51.8, 83.1, 110.1, 117.8, 128.4, 129.2, 129.3, 131.8, 132.6, 136.6, 163.4, 164.8. MS (EI-TOF) *m/z* 361 (M^+, 4%), 311 (38), 254 (37), 222 (100), 134 (67). HRMS (EI-TOF) *m/z* 361.0985 (M^+, $C_{18}H_{19}NO_5S$ requires 361.0984). $[\alpha]_D^{25}$ = + 245 (c 1, CH_2Cl_2). Minor isomer was obtained as colourless needles in 3% yield; mp 143-144 ºC (from hexane-ethyl acetate); IR (KBr) 1743, 1701, 1445, 1170, 1094, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 3H), 3.06 (dd, J = 9.2 and 14.4 Hz, 1H, CH_2Ph), 3.58 (dd, J = 3.6 and 14.4 Hz, 1H, CH_2Ph), 3.80 (s, 3H), 3.81 (s, 3H), 3.95 (d, J = 14.8 Hz, 1H), 4.78 (d, J = 14.8 Hz, 1H), 5.23 (dd, J = 4.0 and 9.2 Hz, 1H, C*H*Bn), 7.09-7.10 (m, 2H, ArH), 7.27-7.32 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 32.8, 48.3, 51.6, 51.7, 71.4, 111.7, 115.7, 127.8, 128.9, 129.2, 129.9, 133.3, 134.5, 163.5, 164.7. MS (EI-TOF) *m/z* 361 (M^+, 10%), 329 (38), 312 (65), 280 (100), 249 (73), 222 (57), 178 (59). HRMS (EI-TOF) *m/z* 361.0983 (M^+, $C_{18}H_{19}NO_5S$ requires 361.0984). $[\alpha]_D^{25}$ = + 85 (*c* 1, CH_2Cl_2).

*4.3.2. Dimethyl 2-oxo-3,5-dimethyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**8b**). This compound*

was prepared in the same manner described above, except that the reaction was carried at room temperature for 30 min. The crude product was purified by flash chromatography [hexane-ethyl acetate (1:1), ethyl acetate, then ethyl acetate-methanol (9:1)]. Compound **8b** was obtained as a white solid in 74% yield. mp 104-105 ºC (from ethyl ether). IR (KBr) 1733, 1705, 1306, 1098, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, J = 7.1 Hz, 3H), 2.42 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 4.26 (d, J = 17.4 Hz, 1H), 4.34 (d, J = 17.4 Hz, 1H), 5.08 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 16.3, 51.0, 51.5, 51.6, 77.8, 110.5, 117.5, 131.5, 134.8, 163.5, 164.8. MS (EI) *m/z* 285 (M^+, 14%), 237 (79), 205 (100), 178 (39), 147 (42), 119 (40). HRMS (EI-TOF) *m/z* 285.0675 (M^+, $C_{12}H_{15}NO_5S$ requires 285.0671).

*4.3.3. Dimethyl 2-oxo-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**18**). This compound was prepared* in the same manner described above, except that the reaction was carried at 0 ºC for 30 min. The product was obtained as colourless oil which crystallizes with ethyl ether to give a white solid in 45% yield. mp 133-135 ºC; IR (KBr) 1722, 1702, 1438, 1287, 1204, 1126, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.84 (s, 3H), 4.32 (d, J = 17.1 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 4.91 (d, J = 12.1 Hz, 1H), 5.08 (d, J = 12.1 Hz, 1H), 7.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.6, 51.7, 53.4, 69.6, 111.1, 121.0, 123.0, 138.0, 163.1, 163.2. MS (EI) *m/z* 257 (M^+, 33%), 225 (29), 209 (100), 194 (36), 178 (20), 164 (22). HRMS (EI-TOF) *m/z* 257.0362 (M^+, $C_{10}H_{11}NO_5S$ requires 257.0358).

4.4. General procedures for generation and trapping of pyrrolo[1,2-*c*]thiazole and pyrazolo[1,5-*c*]thiazole heteropentalenes.

Method A. A solution of the appropriate 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole or 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole (1.02 mmol) and dipolarophile (1.22 mmol) in acetic anhydride (5 mL) was heated to reflux for time indicated in each case. After cooling to room temperature, the solvent was removed in vacuo and the products were isolated by crystallisation and/or flash chromatography.

Method B. A 35 mL sealed tube was charged with the appropriate 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole or 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole (1.11 mmol), dipolarophile (1.33 mmol) and acetic anhydride (5 mL). The reaction mixture was heated at 140 ºC for the time indicated in each case. After cooling to room temperature, the solvent was removed in vacuo and the products were isolated by crystallisation and/or flash chromatography.

Method C. A solution of the appropriate 2-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole or 2-oxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazole (1.14 mmol) and dipolarophile (1.36 mmol) in acetic anhydride (2 mL) was irradiated in the microwave reactor with the temperature and time indicated in each case. After cooling to room temperature, the solvent was removed in vacuo and the products were isolated by crystallisation and/or flash chromatography.

*4.4.1. Dimethyl 1,3-dioxo-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**3a**,* exo*) and (**3b**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by purification by flash

chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, *exo*-adduct **3a** (54%) and *endo*-adduct **3b** (8%) both as solids.

Method B (reaction time: 4 h). Trituration of the residue with ethyl acetate followed by purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, *exo*-adduct **3a** (58%) and *endo*-adduct **3b** (14%).

Method C (temperature set to 180 ºC for 20 min). Purification by flash chromatography [hexane-ethyl acetate (1:1)] gave, in order of elution, *exo*-adduct **3a** (73%) and *endo*-adduct **3b** (10%).

Dimethyl 1,3-dioxo-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***3a***). mp 209-211 ºC (from ethyl ether), lit. 210-211 ºC[2], 210-212 ºC[3]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.48 (d, J = 8.0 Hz, 1H, imide α-H), 3.51 (d, J = 8.0 Hz, 1H, imide α-H), 3.84 (s, 3H), 3.87 (s, 3H), 5.49 (s, 1H, sulphur bridge-H), 6.03 (s, 1H, sulphur bridge-H), 7.25-7.27 (m, 2H, ArH), 7.42-7.52 (m, 3H, ArH).

Dimethyl 1,3-dioxo-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine 7,8-dicarboxylate (***3b***). mp 244-246 ºC (from ethyl ether), lit.[2] 245-247 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.19-4.26 (m, 2H, imide α-H), 5.55 (d, J = 4.0 Hz, 1H, sulphur bridge-H), 6.10 (d, J = 2.4 Hz 1H, sulphur bridge-H), 6.82-6.84 (m, 2H, ArH), 7.33-7.38 (m, 3H, ArH).

*4.4.2. Tetramethyl 4a-methyl-4a,6a-dihydrothiazolo[2,3,4-cd]pyrrolizine-3,4,5,6-tetracarboxylate (**4**).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by recrystallization with the same solvent gave compound **4** as a pale yellow solid (51%).

Method B (reaction time: 4 h). Trituration of the residue with methanol followed by recrystallization with the same solvent gave compoud **4** (35%).

Method C (temperature set to 180 ºC for 20 min). Trituration of the residue with methanol followed by recrystallization with the same solvent gave compound **4** (15%).

*Tetramethyl 4a-methyl-4a,6a-dihydrothiazolo[2,3,4-cd]pyrrolizine-3,4,5,6-tetracarboxylate (**4**).* mp 238-240 ºC lit. 238-240 ºC[2], 239-241 ºC[3]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 3.74 (s, 3H), 3.77 (s, 9H), 4.99 (s, 1H), 5.75 (s, 1H).

*4.4.3. Dimethyl 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrazolo[1,5-a]pyrrolo[3,4-c]pyridine-7,8-dicarboxylate (**5**).*

Method A (reaction time: 7 h). Trituration of the residue with methanol followed by recrystallization with the same solvent gave *exo*-adduct **5** (76%).

Method B (reaction time: 7 h). Trituration of the residue with methanol followed by recrystallization with the same solvent gave *exo*-adduct **5** (71%).

Method C (temperature set to 180 ºC for 15 min). Trituration of the residue with methanol followed by recrystallization with the same solvent gave *exo*-adduct **5** (54%) which was identified by comparison with the specimen previously prepared.

*Dimethyl 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrazolo[1,5-a]pyrrolo[3,4-c]pyridine-7,8-dicarboxylate (**5**).* White solid, mp 199-201 ºC lit.[3] 202-203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, J = 6.0 Hz, 1H, imide α-H), 3.68 (dd, J = 1.2 and 6.4 Hz, 1H, imide α-H), 3.92 (s, 3H),

3.96 (s, 3H), 5.52 (s, 1H, sulphur bridge-H), 6.28 (s, 1H, sulphur bridge-H), 7.25-7.27 (m, 2H, ArH), 7.45-7.52 (m, 3H, ArH).

*4.4.4. Tetramethyl pyrazolo[1,5-a]pyridine-2,3,5,6-tetracarboxylate (**6**).*

Method A (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave compound **6** (45%).

Method B (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave compound **6** (45%).

Method C (temperature set to 180 ºC for 15 min). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave compound **6** (53%).

*Tetramethyl pyrazolo[1,5-a]pyridine-2,3,5,6-tetracarboxylate (**6**).* Yellow solid, mp 99-101 ºC (from ethyl acetate/hexane), lit.[19] 95-97 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 8.40 (s, 1H), 9.00 (s, 1H).

*4.4.5. Non-classical dimethyl 3-benzyl-5-methyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**11**), dimethyl 1,3-dioxo-4-benzyl-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**9a**,* exo*) and (**10a**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by flash chromatography [hexane-ethyl acetate (3:1), (2:1), then (1:1)] gave, in order of elution, **11** (23%), *endo*-adduct **10a** (20%) and *exo*-adduct **9a** (22%).

Method C (temperature set to 160 ºC for 20 min). Purification by flash chromatography [hexane-ethyl acetate (3:1), (2:1), then (1:1)] gave, in order of elution, **11** (36%), *endo*-adduct **10a** (23%) and *exo*-adduct **9a** (10%).

*Non-classical dimethyl 3-benzyl-5-methyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**11**).* White solid, mp 149-150 ºC (from methanol). IR (KBr) 1702, 1581, 1546, 1445, 1408, 1383, 1229, 1177, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.41 (s, 2H), 6.87 (s, 1H), 7.24-7.27 (m, 1H, ArH), 7.37-7.43 (m, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 29.3, 51.5, 52.0, 107.6, 109.4, 119.7, 127.1, 128.0, 128.6, 129.1, 135.4, 136.2, 139.2, 163.6, 165.4. MS (EI) *m/z* 343 (M^+, 50%), 311 (98), 225 (34), 134 (100). HRMS (ESI-TOF) *m/z* 344.0958 ($[M+1]^+$, $C_{18}H_{18}NO_4S$ requires 344.0951).

Dimethyl 1,3-dioxo-4-benzyl-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***10a***). Pale yellow solid, mp 238-240 ºC (from ethyl ether). IR (KBr) 1714, 1388, 1207, 1094 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 3.78 (d, J = 13.6 Hz, 1H), 3.92 (d, J = 8.4 Hz, 1H, imide α-H), 3.98 (dd, J = 4.0 and 8.4 Hz, 1H, imide α–H), 4.38 (d, J = 13.6 Hz, 1H), 5.28 (d, J = 4.0 Hz, 1H, sulphur bridge-H), 6.78-6.80 (m, 2H, ArH), 7.19-7.40 (m, 8H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 35.6, 47.6, 50.6, 50.8, 53.3, 54.4, 89.1, 106.5, 115.2, 125.6, 127.3, 128.1, 128.2, 129.0, 129.6, 130.7, 133.4, 140.2, 161.8, 164.1, 170.4, 171.0. MS (ESI-TOF) *m/z* 539 ($[M+Na]^+$, 100%), 413 (5), 279 (6), 227 (21). HRMS (ESI-TOF) *m/z* 539.1244 ($[M+Na]^+$, $C_{28}H_{24}N_2O_6SNa$ requires 539.1247).

Dimethyl 1,3-dioxo-4-benzyl-6-methyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-

f]indolizine-7,8-dicarboxylate (***9a***). Pale yellow solid, mp 201-203 ºC (from ethyl ether). IR (KBr) 1710, 1390, 1208, 1173, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.34 (d, J = 6.4 Hz, 1H, imide α-H), 3.50 (dd, J = 0.8 and 6.4 Hz, 1H, imide α–H), 3.84 (s, 3H), 3.87 (s, 3H), 4.19 (d, J = 18.0 Hz, 1H), 4.31 (d, J = 18.0 Hz, 1H), 5.44 (bs, 1H, sulfur bridge-H), 7.22-7.32 (m, 8H, ArH), 7.42-7.51 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 36.6, 48.6, 51.6, 51.8, 54.4, 55.4, 90.1, 107.5, 116.2, 126.6, 128.4, 129.1, 129.3, 130.0, 130.7, 131.8, 134.4, 141.3, 162.8, 165.1, 171.4, 172.0. MS (ESI-TOF) *m/z* 539 ($[M+1]^+$, 100%), 517 (24), 336 (6), 245 (6), 201 (35). HRMS (ESI-TOF) *m/z* 517.1419 ($[M+1]^+$, $C_{28}H_{25}N_2O_6S$ requires 517.1428).

*4.4.6. Non-classical dimethyl 3-benzyl-5-methyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**11**), dimethyl 1,3-dioxo-4-benzyl-2,6-dimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**9b**,* exo*) and (**10b**,* endo*).*

Method A (reaction time: 4 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, **11** (21%), *endo*-adduct **10b** (39%) and *exo*-adduct 9b (10%).

Method B (reaction time: 4 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, **11** (16%) and *endo*-adduct **10b** (10%).

Method C (temperature set to 160 ºC for 20 min). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, **11** (16%), *endo*-adduct **10b** (8%) and exo-adduct **9b** (6%).

Compound **11** was characterized by comparison with a specimen previously prepared.

Dimethyl 1,3-dioxo-4-benzyl-2,6-dimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***10b***). Yellow solid, mp 101-103 ºC (from ethyl ether). IR (KBr) 1778, 1703, 1434, 1290, 1210, 1123, 1087 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.57 (s, 3H), 3.77-3.86 (m, 3H, imide α-H and CH_2Ph), 3.80 (s, 3H), 3.83 (s, 3H), 4.40 (d, J = 13.6 Hz, 1H, imide α–H), 5.25 (d, J = 4.0 Hz, 1H, sulfur bridge-H), 7.36-7.45 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 24.5, 36.6, 48.5, 51.6, 51.8, 54.0, 55.4, 90.1, 107.6, 116.1, 128.3, 129.0, 130.0, 131.9, 134.5, 141.2, 162.8, 165.1, 172.4, 172.9. MS (EI-TOF) *m/z* 454 (M^+, 13%), 422 (100), 336 (86). HRMS (EI-TOF) *m/z* 454.1198 (M^+, $C_{23}H_{22}N_2O_6S$ requires 454.1199).

Dimethyl 1,3-dioxo-4-benzyl-2,6-dimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***9b***). Yellow oil. IR (film) 1701, 1437, 1403, 1384, 1297, 1211, 1121, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.05 (s, 3H), 3.19 (d, J = 6.4 Hz, 1H, imide α–H), 3.34-3.36 (m, 1H, imide α–H), 3.82 (s, 3H), 3.86 (s, 3H), 4.14 (d, J = 18.0 Hz, 1H), 4.28 (d, J = 18.0 Hz, 1H), 5.34 (bs, 1H, sulphur bridge-H), 7.27-7.30 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 25.4, 33.3, 49.2, 51.8, 51.9, 53.4, 56.9, 87.2, 106.5, 116.6, 127.5, 128.7, 128.8, 131.3, 135.3, 143.1, 163.2, 165.3, 173.0, 173.8. MS (EI-TOF) *m/z* 454 (M^+, 8%), 422 (100), 336 (86). HRMS (EI-TOF) *m/z* 454.1195 (M^+, $C_{23}H_{22}N_2O_6S$ requires 454.1199).

*4.4.7. Dimethyl 1,3-dioxo-4,6-dimethyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**12a**,* exo*) and (**13a**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by purification by flash

chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution *exo*-adduct **12a** (39%) and *endo*-adduct **13a** (15%).

Method B (reaction time: 4 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave *exo*-adduct **12a** (36%).

Method C (temperature set to 140 ºC for 20 min). Trituration of the residue with methanol followed by purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave *exo*-adduct **12a** (20%).

Dimethyl 1,3-dioxo-4,6-dimethyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***12a***). White solid, mp 223-225 ºC (from ethyl ether). IR (KBr) 1720, 1712, 1692, 1441, 1388, 1200, 1174, 1146, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.50 (s, 3H), 3.28 (d, J = 6.7 Hz, 1H, imide α–H), 3.56 (dd, J = 1.5 and 6.7 Hz, 1H, imide α–H), 3.84 (s, 3H), 3.86 (s, 3H), 5.39 (d, J = 1.5 Hz, 1H, sulphur bridge-H), 7.25-7.28 (m, 2H, ArH), 7.46-7.50 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 17.1, 50.5, 51.8, 51.9, 53.6, 56.6, 83.4, 106.4, 115.6, 126.4, 129.2, 129.3, 131.1, 131.5, 142.8, 163.2, 165.4, 171.9, 173.1. MS (EI) *m/z* 440 (M^+, 38%), 408 (28), 267 (100). HRMS (ESI-TOF) *m/z* 441.1102 ($[M+1]^+$, $C_{22}H_{21}N_2O_6S$ requires 441.1115).

Dimethyl 1,3-dioxo-4,6-dimethyl-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***13a***). Pale yellow solid, mp 233-235 ºC (from dichloromethane/methanol). IR (KBr) 1780, 1718, 1444, 1389, 1211, 1144, 1087 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.50 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.95 (d, J = 8.3 Hz, 1H, imide α–H), 4.31 (dd, J = 4.2 and 8.3 Hz, 1H, imide α–H), 5.44 (d, J = 4.2 Hz, 1H, sulphur bridge-H), 6.82-6.86 (m, 2H, ArH), 7.35-7.38 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 18.1, 50.3, 51.6, 51.7, 56.0, 59.1, 84.0, 107.6, 115.7, 126.6, 129.1, 129.2, 130.6, 132.0, 140.6, 162.8, 165.0, 171.2, 171.5. MS (EI) *m/z* 440 (M^+, 37%), 408 (26), 267 (100). HRMS (ESI-TOF) *m/z* 463.0952 ($[M+Na]^+$, $C_{22}H_{20}N_2O_6SNa$ requires 463.0934).

*4.4.8. Dimethyl 1,3-dioxo-2,4,6-trimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**12b**,* exo*) and (**13b**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, *exo*-adduct **12b** (19%) and *endo*-adduct **13b** (23%).

Method B (reaction time: 4 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave, in order of elution, *exo*-adduct **12b** (20%) and *endo*-adduct **13b** (19%).

Dimethyl 1,3-dioxo-2,4,6-trimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***12b***). Pale yellow solid, mp 186-188 ºC (from ethyl acetate/hexane). IR (KBr) 1781, 1711, 1436, 1299, 1203, 1142, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.47 (s, 3H), 3.03 (s, 3H), 3.14 (d, J = 6.4 Hz, 1H, imide α–H), 3.40 (approx. d, J = 6.0 Hz, 1H, imide α–H), 3.82 (s, 3H), 3.84 (s, 3H), 5.28 (bs, 1H, sulphur bridge-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.1, 25.3, 50.0, 51.7, 51.8, 53.7, 56.7, 83.0, 106.2, 115.4, 131.1, 142.9, 163.2, 165.3, 172.9, 174.0. MS (EI) *m/z* 378 (M^+, 34%), 346 (32), 267 (100), 177 (20), 149 (18). HRMS (EI-TOF) *m/z* 378.0888 (M^+, $C_{17}H_{18}N_2O_6S$ requires 378.0886).

Dimethyl 1,3-dioxo-2,4,6-trimethyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***13b***). Yellow oil. IR (film) 1702, 1434, 1402, 1290, 1211, 1090 cm^{-1}. ^1H NMR (400 MHz,

$CDCl_3$) δ 2.31 (s, 3H), 2.39 (s, 3H), 2.46 (s, 3H), 3.66 (d, J = 8.0 Hz, 1H, imide α–H), 3.71 (s, 3H), 3.75 (s, 3H), 4.01-4.06 (m, 1H, imide α–H), 5.28 (d, J = 4.0 Hz, 1H, sulfur bridge-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 18.1, 24.5, 50.2, 51.6, 51.7, 56.0, 58.7, 84.0, 107.6, 115.6, 132.1, 140.5, 162.9, 165.1, 172.2, 172.4. MS (EI) *m/z* 378 (M^+, 35%), 346 (33), 267 (100), 177 (22), 149 (18). HRMS (EI-TOF) *m/z* 378.0886 (M^+, $C_{17}H_{18}N_2O_6S$ requires 378.0886).

*4.4.9. Dimethyl 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**19a**, exo) and (**20a**, endo) and dimethyl 5,7-dioxo-6-phenyl-4b,5,6,7,7a,7b-hexahydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine-3,4-dicarboxylate (**21a**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with methanol followed by purification by flash chromatography [hexane-ethyl acetate (2:1), (1:1), then (1:2)] gave, in order of elution, *exo*-adduct **19a** (33%) and *endo*-adduct **21a** (18%).

Method B (reaction time: 4 h). Trituration of the residue with methanol followed by purification by flash chromatography [hexane-ethyl acetate (2:1), (1:1), then (1:2)] gave, in order of elution, *exo*-adduct **19a** (28%) and a mixture of *endo*-adduct **20a** (7%) and *endo*-adduct **21a** (12%). The *endo*-adduct **21a** was isolated from the mixture by selective crystallization with ethyl acetate.

Method C (temperature set to 180 ºC for 20 min). Trituration of the residue with methanol gave *exo*-adduct **19a** (55%). Purification of the residue by flash chromatography [hexane-ethyl acetate (1:1)] gave *endo*-adduct **20a** (13%).

Dimethyl 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***19a***). White solid, mp 207-209 ºC (from ethyl ether). IR (KBr) 1737, 1720, 1382, 1284, 1187, 1070 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (dd, J = 0.8 and 6.8 Hz, 1H, imide α-H), 3.56 (dd, J = 1.2 and 6.8 Hz, 1H, imide α–H), 3.83 (s, 3H), 3.90 (s, 3H), 5.55 (s, 1H, sulphur bridge-H), 6.01 (s, 1H, sulfur bridge-H), 7.25-7.26 (m, 2H, ArH), 7.36 (s, 1H), 7.44-7.52 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.0, 51.8, 52.0, 52.2, 53.5, 69.6, 108.3, 118.0, 121.6, 126.4, 129.3, 129.4, 131.4, 143.1, 162.7, 163.4, 172.2, 172.9. MS (EI) *m/z* 412 (M^+) (7), 239 (100), 202 (22). HRMS (EI-TOF) *m/z* 412.0724 (M^+, $C_{20}H_{16}N_2O_6S$ requires 412.0729).

Dimethyl 5,7-dioxo-6-phenyl-4b,5,6,7,7a,7b-hexahydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine-3,4-dicarboxylate (***21a***). White solid, mp 248-250 ºC. IR (KBr) 1719, 1386, 1301, 1203, 1106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 4.28 (d, J = 13.6 Hz, 1H, H-2), 4.33 (approx. t, J = 7.6 Hz, 1H, H-7a), 4.78 (d, J = 13.6 Hz, 1H, H-2), 4.89 (d, J = 6.8 Hz, 1H, H-4b), 6.08 (d, J = 7.6 Hz, 1H, H-7b), 7.19-7.21 (m, 2H, ArH), 7.36-7.46 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.5, 50.8, 51.7, 52.0, 53.2, 60.3, 115.5, 115.7, 126.3, 129.1, 129.2, 131.0, 131.2, 138.6, 162.7, 163.0, 169.9, 170.6. MS (EI) *m/z* 412 (M^+, 42%), 380 (100), 261 (26), 233 (79), 147 (42). HRMS (EI-TOF) *m/z* 412.0730 (M^+, $C_{20}H_{16}N_2O_6S$ requires 412.0729).

Dimethyl 1,3-dioxo-2-phenyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***20a***). Yellow oil. IR (KBr) 1716, 1499, 1384, 1290, 1186, 1105, 1065 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.85 (s, 3H), 4.22 (dd, J = 2.8 and 8.4 Hz, 1H, imide α-H), 4.27 (dd, J = 4.0 and 8.4 Hz, 1H, imide α–H), 5.60 (d, J = 3.6 Hz, 1H, sulphur bridge-H), 6.10 (d, J = 2.4 Hz, 1H, sulphur bridge-H), 6.81-6.83 (m, 2H, ArH), 7.27 (s, 1H), 7.34-7.36 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ

51.7, 51.8, 52.0, 53.6, 56.2, 69.5, 108.9, 118.2, 122.4, 126.4, 129.1, 129.2, 130.5, 140.9, 162.3, 163.2, 171.0, 171.2. MS (EI) *m/z* 412 (M^+, 4%), 378 (16), 347 (18), 239 (100), 208 (11), 202 (10). HRMS (EI-TOF) *m/z* 412.0727 (M^+, $C_{20}H_{16}N_2O_6S$ requires 412.0729).

*4.4.10. Dimethyl 1,3-dioxo-2-methyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**19b**,* exo*) and (**20b**,* endo*) and dimethyl 5,7-dioxo-6-methyl-4b,5,6,7,7a,7b-hexahydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine-3,4-dicarboxylate (**21b**,* endo*).*

Method A (reaction time: 4 h). Trituration of the residue with ethyl acetate gave *exo*-adduct **19b** (20%). Purification of the residue by flash chromatography [hexane-ethyl acetate (1:1), (1:2), then ethyl acetate] gave a mixture of *endo*-adduct **20b** (9%) and *endo*-adduct **21b** (27%). Compound **21b** was isolated from the mixture by selective crystallization with ethyl acetate.

Method B (reaction time: 4 h). Trituration of the residue with ethyl acetate gave *exo*-adduct **19b** (19%). Purification of the residue by flash chromatography [hexane-ethyl acetate (1:1), (1:2), then (1:3)] gave a mixture of *endo*-adduct **20b** (2%) and *endo*-adduct **21b** (16%).

Method C (temperature set to 180 ºC for 20 min). Trituration of the residue with ethyl acetate gave *exo*-adduct **19b** (19%). Purification of the residue by flash chromatography [hexane-ethyl acetate (1:1), (1:2), then (1:3)] gave a mixture of *endo*-adduct **20b** (8%) and *endo*-adduct **21b** (26%).

Dimethyl 1,3-dioxo-2-methyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***19b***). White solid, mp 256-258 ºC (from methanol). IR (KBr) 1736, 1692, 1439, 1383, 1288, 1181, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.36 (d, J = 6.8 Hz, 1H, imide α-H), 3.40 (d, J = 6.8 Hz, 1H, imide α–H), 3.82 (s, 3H), 3.89 (s, 3H), 5.43 (s, 1H, sulphur bridge-H), 5.95 (s, 1H, sulphur bridge-H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 51.1, 51.7, 51.8, 52.0, 53.6, 69.2, 108.1, 118.0, 121.5, 143.2, 162.7, 163.4, 173.0, 173.8. MS (EI) *m/z* 350 (M^+, 54%), 318 (100), 291 (26), 260 (20), 233 (39), 147 (21). HRMS (EI-TOF) *m/z* 350.0579 (M^+, $C_{15}H_{14}N_2O_6S$ requires 350.0573).

Dimethyl 1,3-dioxo-2-methyl-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (***20b***). Yellow oil. IR (film) 1781, 1705, 1435, 1383, 1290, 1208, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 4.04 (dd, J = 3.2 and 8.0 Hz, 1H, imide α-H), 4.10 (dd, J = 4.0 and 8.0 Hz, 1H, imide α–H), 5.49 (d, J = 4.0 Hz, 1H, sulphur bridge-H), 6.03 (d, J = 3.2 Hz, 1H, sulphur bridge-H), 7.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 51.6, 51.8, 51.9, 53.6, 55.9, 69.4, 108.8, 117.9, 122.5, 140.8, 162.4, 163.2, 171.9, 172.0. MS (EI) *m/z* 350 (M^+, 57%), 318 (100), 291 (29), 260 (20), 233 (40), 147 (21). HRMS (EI-TOF) *m/z* 350.0571 (M^+, $C_{15}H_{14}N_2O_6S$ requires 350.0573).

Dimethyl 5,7-dioxo-6-methyl-4b,5,6,7,7a,7b-hexahydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine-3,4-dicarboxylate (***21b***). White solid, mp 222-223 ºC. IR (KBr) 1777, 1731, 1697, 1434, 1300, 1119, 1103 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.96 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 4.16 (approx. t, J = 7.6 Hz, 1H, H-7a), 4.24 (d, J = 14.0 Hz, 1H, H-2), 4.73-4.74 (m, 2H, H-2 and H-4b), 6.00 (d, J = 7.6 Hz, 1H, H-7b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 37.4, 50.9, 51.7, 52.0, 53.2, 60.0, 115.3, 115.5, 131.4, 138.2, 162.8, 163.0, 171.0, 171.7. MS (EI) *m/z* 350 (M^+, 15%), 319 (9), 239 (100), 208 (14). HRMS (EI-TOF) *m/z* 350.0574 (M^+, $C_{15}H_{14}N_2O_6S$ requires 350.0573.

*4.4.11. 5,7(4bH,6H)-Dioxo-6-phenyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (**26a**, exo) and (**27a**, endo).*

Method A (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (3:1)] gave, in order of elution, *exo*-adduct **26a** (11%) and *endo*-adduct **27a** (30%).

Method B (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (3:1), then (2:1)] gave, in order of elution, *exo*-adduct **26a** (10%) and *endo*-adduct **27a** (26%).

5,7(4bH,6H)-Dioxo-6-phenyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (***26a***). Colourless needles, mp 191-193 ºC (from ethyl ether). IR (KBr) 1716, 1392, 1241, 1174, 1109, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (d, J = 13.6 Hz, 1H, H-2), 4.35 (dd, J = 5.6 and 8.4 Hz, 1H, H-7a), 4.65 (d, J = 8.8 Hz, 1H, H-4b), 4.76 (d, J = 13.6 Hz, 1H, H-2), 5.95 (d, J = 5.6 Hz, 1H, H-7b), 6.25 (s, 1H), 7.30-7.32 (m, 2H, ArH), 7.43-7.53 (m, 3H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0, 49.6, 57.8, 61.9, 107.9 (q, $J_{C\text{-}C\text{-}CF3}$ = 3.0 Hz), 115.5 (q, $J_{C\text{-}CF3}$ = 37.4 Hz), 122.7 (q, $J_{C\text{-}F3}$ = 265 Hz), 126.4, 129.2, 129.4, 130.7, 131.2, 134.3 (q, $J_{C\text{-}C\text{-}CF3}$ = 4.7 Hz), 171.4, 172.3. MS (ESI-TOF) *m/z* 365 ($[M+1]^+$, 100%). HRMS (ESI-TOF) *m/z* 365.0563 ($[M+1]^+$, $C_{17}H_{12}N_2O_2F_3S$ requires 365.0566).

5,7(4bH,6H)-Dioxo-6-phenyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (***27a***). White solid, mp 232-233 ºC (from ethyl acetate-hexane). IR (KBr) 1722, 1492, 1376, 1239, 1186, 1101, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (d, J = 13.6 Hz, 1H, H-2), 4.28 (approx. t, J = 7.2 Hz, 1H, H-7a), 4.72 (d, J = 6.8 Hz, 1H, H-4b), 4.77 (d, J = 13.6 Hz, 1H, H-2), 6.09 (d, J = 7.6 Hz, 1H, H-7b), 6.17 (s, 1H), 7.21-7.23 (m, 2H, ArH), 7.34-7.48 (m, 3H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.2, 50.4, 54.1, 59.5, 103.0 (q, $J_{C\text{-}C\text{-}CF3}$ = 2.7 Hz), 112.4 (q, $J_{C\text{-}CF3}$ = 36.8 Hz), 123.1 (q, $J_{C\text{-}F3}$ = 266 Hz), 126.6, 128.6, 129.0, 131.7, 133.2 (q, $J_{C\text{-}C\text{-}CF3}$ = 4.9 Hz), 172.5, 172.9. MS (EI) *m/z* 364 (M^+, 100%), 217 (35), 188 (73), 177 (12). HRMS (ESI-TOF) *m/z* 365.0563 ($[M+1]^+$, $C_{17}H_{12}N_2O_2F_3S$ requires 365.0566).

*4.4.12. 5,7(4bH,6H)-Dioxo-6-methyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (**27b**, endo).*

Method A (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (2:1)] gave *endo*-adduct **27b** (50%).

Method B (reaction time: 7 h). Purification by flash chromatography [hexane-ethyl acetate (2:1), then (1:1)] gave *endo*-adduct **27b** (63%).

5,7(4bH,6H)-Dioxo-6-methyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (**27b**, endo). White solid, mp 189-191 ºC (from ethyl ether). IR (KBr) 1711, 1431, 1376, 1283, 1246, 1226, 1167, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 3.97 (d, J = 13.3 Hz, 1H, H-2), 4.13 (approx. t, J = 7.2 Hz, 1H, H-7a), 4.58 (d, J = 6.7 Hz, 1H, H-4b), 4.74 (d, J = 13.3 Hz, 1H, H-2), 6.02 (d, J = 7.5 Hz, 1H, H-7b), 6.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 35.9, 50.0, 54.0, 59.6, 105.1 (q, $J_{C\text{-}C\text{-}CF3}$ = 3.2 Hz), 115.2 (q, $J_{C\text{-}CF3}$ = 37.5 Hz), 122.7 (q, $J_{C\text{-}F3}$ = 265 Hz), 130.2, 132.2 (q, $J_{C\text{-}C\text{-}CF3}$ = 4.7 Hz), 172.4, 172.9. MS (EI) *m/z* 302 (M^+, 100%), 283 (11), 217 (44), 197 (14), 188 (19), 172 (11), 148 (11). HRMS (EI-TOF) *m/z* 302.0335 (M^+, $C_{12}H_9N_2O_2F_3S$ requires 302.0337).

4.5. General procedure for the synthesis of dimethyl 1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-

***f*]indolizine-7,8-dicarboxylates.**

Method A. A solution of sodium (11 mg, 0.46 mmol) dissolved in anhydrous methanol (2 mL) was added slowly to a solution of the appropriate dimethyl 1,3-dioxo-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[3,4-*f*]indolizine-7,8-dicarboxylate (0.23 mmol) in anhydrous dichloromethane (5 mL). After stirring at room temperature for 1.5 h, the reaction was quenched with saturated aqueous ammonium chloride solution (5 mL). The organic phase was separated, dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product was purified by flash chromatography [hexane-ethyl acetate].
Method B. A solution of potassium *tert*-butoxide (78 mg, 0.66 mmol) in anhydrous *tert*-butanol (2 mL) was added slowly to a solution of the appropriate dimethyl 1,3-dioxo-4,9-epithio-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[3,4-*f*]indolizine-7,8-dicarboxylate (0.33 mmol) in anhydrous dichloromethane (8 mL). After stirring at room temperature for 0.5 h, the reaction was quenched with saturated aqueous ammonium chloride solution (5 mL). The organic phase was separated, dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product was purified crystallization or flash chromatography [hexane-ethyl acetate].

*4.5.1. Dimethyl 4-benzyl-6-methyl-1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**14a**).* This compound was prepared by method A and was obtained as a yellow solid (38%), mp 235-237 ºC (from ethyl ether). IR (KBr) 1768, 1713, 1686, 1452, 1398, 1371, 1259, 1164, 1068 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 5.29 (bs, 2H), 6.96-6.99 (m, 2H, ArH), 7.25-7.30 (m, 2H, ArH), 7.40-7.50 (m, 6H, ArH), 8.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 32.7, 52.1, 52.8, 109.5, 115.3, 116.9, 122.4, 125.8, 126.6, 127.1, 128.4, 128.8, 129.1, 129.4, 131.6, 136.1 137.1, 140.7, 163.1, 164.6, 166.0, 166.1. MS (ESI-TOF) *m/z* 505 ($[M+Na]^+$, 63%), 483 $[M+1]^+$ (49), 319 (15), 201 (100). HRMS (ESI-TOF) *m/z* 483.1539 ($[M+1]^+$, $C_{28}H_{23}N_2O_6$ requires 483.1551).

*4.5.2. Dimethyl 4,6-dimethyl-1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**14b**).* This compound was prepared by method B, except that *tert*-butanol was replaced by methanol as solvent. Recrystallization with ethyl acetate/hexane gave **14b** as an orange solid (87%), mp 233-235 ºC. IR (KBr) 1763, 1704, 1457, 1397, 1388, 1236, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 3H), 3.38 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 7.42-7.44 (m, 3H, ArH), 7.50-7.54 (m, 2H, ArH), 8.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 15.9, 52.0, 52.8, 108.9, 113.8, 116.1, 122.9, 125.6, 126.7, 128.4, 128.9, 129.1, 131.7, 135.7, 140.6, 163.0, 164.6, 166.1, 166.5. MS (EI) *m/z* 406 (M^+, 44%), 374 (34), 288 (100). HRMS (ESI-TOF) *m/z* 407.1238 ($[M+1]^+$, $C_{22}H_{19}N_2O_6$ requires 407.1238.

*4.5.3. Dimethyl 2,4,6-trimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**14c**).* This compound was prepared by method B, except that *tert*-butanol was replaced by tetrahydrofuran as solvent. Purification by flash chromatography gave **14c** as a yellow solid (50%), mp 210-212 ºC (from ethyl ether). IR (KBr) 1760, 1733, 1706, 1429, 1392, 1291, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3H), 3.19 (s, 3H), 3.32 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 8.49 (s, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 15.4, 15.8, 24.4, 51.9, 52.8, 108.7, 114.2, 115.4, 123.3, 125.4, 128.8, 135.6, 139.7, 163.1, 165.7, 166.1, 167.5. MS (EI-TOF) *m/z* 344 (M^+, 15%), 312 (33), 254 (15), 226 (100). HRMS (EI-TOF) *m/z* 344.1005 (M^+, $C_{17}H_{16}N_2O_6$ requires 344.1008).

*4.5.4. Dimethyl 1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**22a**).* This compound was prepared by method B. Purification by flash chromatography gave compound **22a** as a pale yellow solid (35%), mp 217-219 ºC (from ethyl ether). IR (KBr) 1770, 1721, 1711, 1385, 1240, 1119. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 4.00 (s, 3H), 7.43-7.46 (m, 3H), 7.52-7.56 (m, 2H), 7.94 (s, 1H), 8.61 (s, 1H), 8.72 (s, 1H). MS (EI) *m/z* 378 (M^+, 82%), 347 (100), 317 (25), 168 (15). HRMS (ESI-TOF) *m/z* 407.1238 ($[M+1]^+$, $C_{22}H_{19}N_2O_6$ requires 407.1238).

*4.5.5. Dimethyl 2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate (**22b**).* This compound was prepared by method B. Purification by flash chromatography gave compound **22b** as a white solid (38%), mp 220-222 ºC (from ethyl ether). IR (KBr) 1766, 1736, 1708, 1431, 1210 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 7.88 (s, 1H), 8.49 (s, 1H), 8.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 52.1, 52.6, 110.5, 117.6, 117.9, 121.2, 123.4, 123.9, 124.3, 134.8, 163.0, 163.6, 165.6, 165.8. MS (EI) *m/z* 316 (M^+, 60%), 298 (44), 285 (95), 255 (43), 240 (23), 212 (100). HRMS (EI) *m/z* 316.0693 (M^+, $C_{15}H_{12}N_2O_6$ requires 316.0695).

4.6. Crystal-structure determination of 11 and 27a.

Crystals of compounds **11** and **27a** were selected, covered with polyfluoroether oil, and mounted on a nylon loop. Crystallographic data for both compounds were collected at the IST using graphite monochromated Mo-Kα radiation (λ=0.71073Å) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat, at 150 K. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all observed reflections. Absorption corrections were applied using SADABS.[21] Structure solution and refinement were performed using direct methods with the program SIR2004[22] included in the package of programs WINGX-Version 1.80.05[23] and SHELXL.[24] All hydrogen atoms were inserted in idealized positions and allowed to refine riding on the parent carbon atom. Figures of the molecular structures were generated using ORTEP-III.[25]

*4.6.1. Crystallographic data for non-classical 3-benzyl-5-methyl-1H,3H-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**11**):* $C_{18}H_{17}NO_5S$, *M* = 359.39, monoclinic, *Cc* with unit cell, *a* = 11.8618(19) Å, *b* = 21.454(3) Å, *c* = 7.3253(12) Å, α = 90°, β = 120.633(7)°, γ = 90°, *V* = 1604.0(4) $Å^3$. It contains four molecules/unit cell. ρcalcd. = 1.488 g cm^{-3}, *Z* = 4, μ = 0.232 mm^{-1}. *R* [$I>2\sigma(I)$] = 0.0806 and *R*w = 0.2126 for 2171 independent reflections.

*4.6.2 Crystallographic data for 5,7(4bH,6H)-dioxo-6-phenyl-3-(trifluoromethyl)-7a,7b-dihydro-2H-pyrrolo[3',4':5,6]thiazolo[2,3,4-cd]pyrrolizine (**27a**):* $C_{17}H_{11}F_3N_2O_2S$, *M* = 364.34, triclinic, *P*-1 with unit cell, *a* = 8.9513(5) Å, *b* = 9.2025(5) Å, *c* = 9.8159(6) Å, α = 79.646(4)°, β = 76.155(3)°, γ = 71.164(4)°, *V*

= 738.41(7) Å^3. It contains two molecules/unit cell. ρcalcd. = 1.639 g cm^{-3}, Z = 2, μ = 0.269 mm^{-1}. R [I>2σ(I)] = 0.0300 and Rw = 0.0729 for 2652 independent reflections.

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Supplementary data

Supplementary Information available: ^{1}H and ^{13}C NMR spectra of the new compounds and selected bond lengths and angles of compounds **11** and **27a** determined by X-ray crystallography. See DOI: xxxx

Notes and references

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