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Cycloaddition reactions of 3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates

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Abstract—Intermolecular 1,3-dipolar cycloaddition of (5*R*)- and (5*S*)-3,5-diphenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates, (5*R*)- and (5*S*)-3-(*p*-methoxyphenyl)-5-phenyl-5*H*,7*H*-thiazolo-[3,4-*c*]oxazol-4-ium-1-olates with a range of dipolarophiles is described. New chiral 5-aryl-3-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles with *R* and *S* configuration were obtained. The structure of methyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate was determined by X-ray crystallography. The synthesis of 7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates was also achieved.

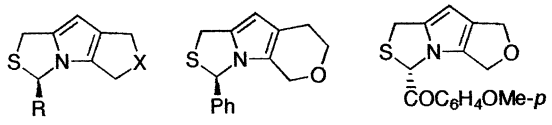
1. Introduction

The dipolar cycloaddition of münchnones (oxazolium-5-olates) represents a particularly attractive approach to the synthesis of pyrroles. These mesoionic rings act as masked cyclic azomethine ylides on reacting with a variety of double and triple bond dipolarophiles providing an initial cycloadduct that usually releases carbon dioxide. Bicyclic mesoionic ring systems provide a route to heterocycles in which another ring system is annulated to pyrrole.[1]

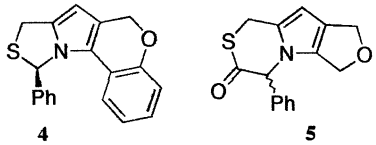
We have been interested in the development of this type of approach for the synthesis of chiral 1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole derivatives, heterocyclic compounds with potential biological activity.[2,3] The cyclodehydration of *N*-acylthiazolidine-4-carboxylic acids was used to generate bicyclic münchnones, 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates, which participated in intramolecular and intermolecular 1,3-dipolar addition.[3]

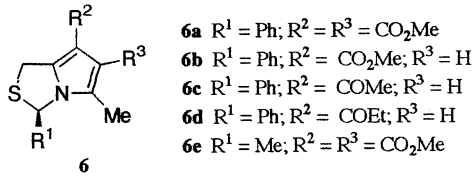
The study of the reactivity of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles allowed us to describe the first examples of intramolecular 1,3-dipolar cycloaddition of this type of münchnones. The synthesis of chiral pyrrolo[1,2-*c*]thiazoles **1**–**4** and an interesting rearrangement to pyrrolo[1,2-*c*]-[1,4]thiazine **5** was achieved.[3a,c]

The intermolecular dipolar cycloaddition of (5*R*)-3-methyl-

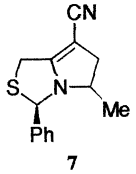


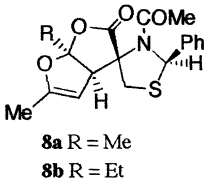
1a R = Ph; X = O
1b R = Ph; X = S
1c R = Me; X = O
1d R = COC_6H_4-OMe-*p*; X = O
1e R = COPh; X = O





6a R^1 = Ph; R^2 = R^3 = CO_2Me
6b R^1 = Ph; R^2 = CO_2Me; R^3 = H
6c R^1 = Ph; R^2 = COMe; R^3 = H
6d R^1 = Ph; R^2 = COEt; R^3 = H
6e R^1 = Me; R^2 = R^3 = CO_2Me





8a R = Me
8b R = Et

Keywords: dipolar cycloaddition; münchnones; 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles.

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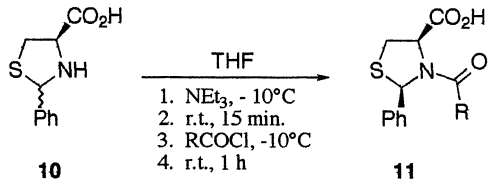
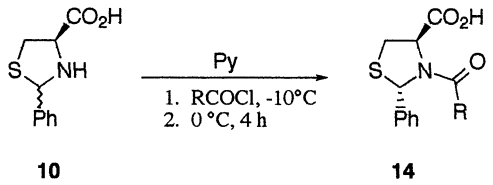


11a R = Ph 76%
11b R = C_6H_4OMe-*p* 50%

Scheme 1.

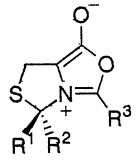


14a R = Ph 44%
14b R = C_6H_4OMe-*p* 75% (d.e. 50%)

Scheme 3.

5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate led to a range of new chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives (**6a**–**6e** and **7**) and new spiro compounds (**8a** and **8b**) were also obtained.[3b,3c]

In this paper we describe the generation and reactivity of (5*R*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates (**9a** and **9c**) and (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo-[3,4-*c*]oxazol-4-ium-1-olates (**9b** and **9d**) towards dipolarophiles.



9a R^1 = Ph; R^2 = H; R^3 = Ph
9b R^1 = H; R^2 = Ph; R^3 = Ph
9c R^1 = Ph; R^2 = H; R^3 = C_6H_4OMe-*p*
9d R^1 = H; R^2 = Ph; R^3 = C_6H_4OMe-*p*

The objective of this work is to broaden the scope of the münchnones cycloaddition approach to chiral pyrrolo[1,2-*c*]-thiazoles and to study the effect of the nature of the mesoionic ring substituent at C-3 on the reactivity.

2. Results and discussion

The synthetic strategy we want to explore requires the synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylic acids in diastereoisomeric pure form to generate the bicyclic münchnones which, on reacting with dipolarophiles enable the synthesis of chiral pyrrolo[1,2-*c*]thiazoles.

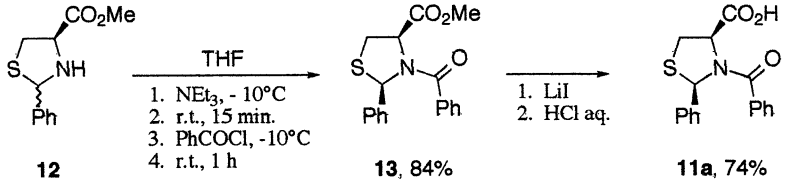
2-Substituted-1,3-thiazolidine-4-carboxylic acids are obtained as mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomers from the reaction of aldehydes and L-cysteine. The acylation of the diastereoisomeric mixture with acetic anhydride or with acid chlorides can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (2*R*,4*R*) or (2*S*,4*R*) stereochemistry depending on the reaction conditions.[4]

In order to obtain *N*-acyl-2-phenyl-1,3-thiazolidine-4-carboxylic acids with (2*R*,4*R*) stereochemistry we used an experimental procedure described in the literature for the synthesis of (2*R*,4*R*)-*N*-carbethoxy-2-phenyl-1,3-thiazolidine-4-carboxylic acid.[4c] Thus, the *cis* derivatives **11a** (76%) and **11b** (50%) were obtained selectively by treating with the appropriate acid chloride (benzoyl chloride and *p*-methoxybenzoyl chloride) the triethylamine salt of thiazolidine **10** in tetrahydrofuran (Scheme 1).

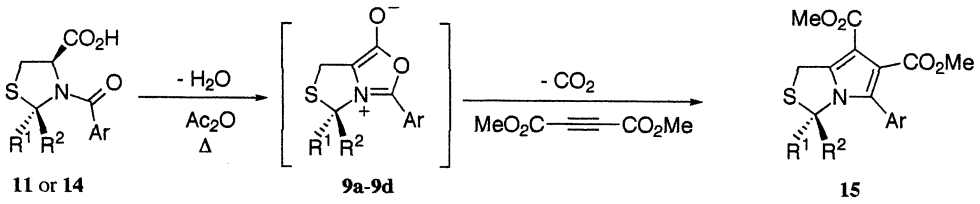
Our previous studies indicated that direct acylation of 2-phenylthiazolidine-4-carboxylic acid with acid chlorides usually leads to a complex mixture of products and more efficient synthesis were obtained promoting the *N*-acylation of methyl 2-phenyl-1,3-thiazolidine-4-carboxylate **12** followed by its conversion into the corresponding acid by the reaction with lithium iodide in ethyl acetate and treatment with aqueous HCl.[3a] Compound **11a** was prepared by this route, using benzoyl chloride as the acylating agent, but the overall yield was only 62% (Scheme 2).

It is known that NMR spectra of *N*-acylthiazolidines at ambient temperature are complicated by the existence of rotamers but the spectrum is simpler at higher temperature.[3a,4] In agreement with this we found that the ^{1}H NMR spectra of thiazolidines **11a** and **13**, recorded at room temperature, showed very broad lines but when recorded at 50°C, showed a single sharp set of signals.

Attempts were made to synthesise *N*-benzoyl-2-phenyl-1,3-thiazolidine-4-carboxylic acid **14a** with (2*S*,4*R*) stereochemistry treating at −40°C, a solution of thiazolidine **10** in dry pyridine with benzoyl chloride as described in the literature for the synthesis of (2*S*,4*R*)-*N*-carbethoxy-2-phenyl-1,3-thiazolidine-4-carboxylic acid.[4c] Under these conditions only starting thiazolidine could be recovered. However, when the addition of the acid chloride was



Scheme 2.



11a R^1 = H; R^2 = Ph; Ar = Ph
14a R^1 = Ph; R^2 = H; Ar = Ph
11b R^1 = H; R^2 = Ph; Ar = C_6H_4OMe-*p*
14b R^1 = Ph; R^2 = H; Ar = C_6H_4OMe-*p*

15a R^1 = H; R^2 = Ph; Ar = Ph 90%
15b R^1 = Ph; R^2 = H; Ar = Ph 83%
15c R^1 = H; R^2 = Ph; Ar = C_6H_4OMe-*p* 85%
15d R^1 = Ph; R^2 = H; Ar = C_6H_4OMe-*p* 92%

Scheme 4.

made at −10°C and the reaction mixture was stirred at 0°C for 4 h thiazolidine **14a** was obtained selectively in moderate yield, 44% (Scheme 3).

Using the same reaction conditions *N*-(*p*-methoxybenzoyl)-2-phenylthiazolidine-4-carboxylic acid was obtained as a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-isomers (75%, d.e. 50%). From this, pure (2*S*,4*R*)-*N*-(*p*-methoxybenzoyl)-2-phenylthiazolidine-4-carboxylic acid **14b** was obtained by flash chromatography (overall yield 25%).

Münchnones **9a**–**9d** were generated and their dipolar cycloaddition with dimethyl acetylenedicarboxylate studied by heating a solution of the appropriated *N*-aroyl-2-phenylthiazolidine-4-carboxylic acid in acetic anhydride in the presence of this dipolarophile (Scheme 4).

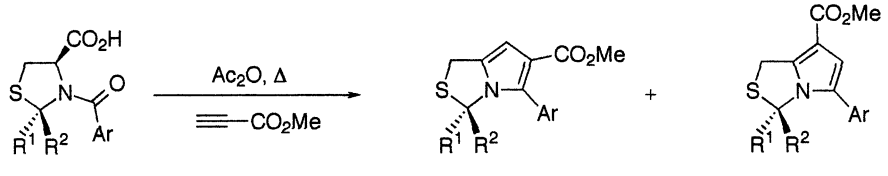
The reaction of (5*R*)-3,5-diphenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **9a** gave chiral (3*R*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **15a** in 90% yield ($[\alpha]_D^{25}$=+201). Starting from (2*S*,4*R*)-*N*-benzoyl-2-phenyl-1,3-thiazolidine-4-carboxylic acid (**14a**) the synthesis of (3*S*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6,7-dicarboxylate **15b** ($[\alpha]_D^{25}$=−209) was achieved in 83% yield. The CD spectra of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **15a** and **15b** were recorded confirming these compounds as an enantiomeric pair.

The cycloadditions of (5*R*)-3-(*p*-methoxybenzoyl)-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **9c** with dimethyl acetylenedicarboxylate gave chiral (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **15c** in 85% yield ($[\alpha]_D^{25}$=+230). (3*S*)-3-Phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **15d** ($[\alpha]_D^{25}$=−224), enantiomer of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **15c**, was also prepared in 92% yield from the cycloaddition of (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **9d**.

The dipolar cycloaddition of the bicyclic mesoionic ring systems **9a**–**9d** with the dipolarophile methyl propiolate was also investigated (Scheme 5).

Treatment of carboxylic acid **11a** with methyl propiolate under cycloaddition reaction conditions gave regioisomers **16a** and **17a** in a 62:38 mixture and 68% yield. 1*H*,3*H*-Pyrrolo[1,2-*c*]thiazoles **16b** and **17b** (64:36), were also obtained from the reaction of (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **9b** with methyl propiolate in 55% yield. The reaction of münchnone **9c** gave 3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6-carboxylates **16c** and **17c** (70:30) in 55% yield. The new chiral (3*S*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate **16d** and (3*S*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylate **17d** (79:21) were synthetised from **9d** in 47% yield. In all four cases the major component (**16**) could be separated from the mixture (**16/17**) by selective crystallisation with ethyl ether–hexane.

Györgydeák et al.[5] have reported that the ^{1}H NMR spectra of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate derivatives show the C-3 proton coupled with one of the C-1 protons. The same type of coupling is observed in the ^{1}H NMR spectra of compounds **15a**–**15d** (*J*∼1.6 Hz).



11a R^1 = H; R^2 = Ph; Ar = Ph
14a R^1 = Ph; R^2 = H; Ar = Ph
11b R^1 = H; R^2 = Ph; Ar = C_6H_4OMe-*p*
14b R^1 = Ph; R^2 = H; Ar = C_6H_4OMe-*p*

	(16:17)
16a,17a R^1 = H; R^2 = Ph; Ar = Ph	68% (62:38)
16b, 17b R^1 = Ph; R^2 = H; Ar = Ph	55% (64:36)
16c, 17c R^1 = H; R^2 = Ph; Ar = C_6H_4OMe-*p*	55% (70:30)
16d, 17d R^1 = Ph; R^2 = H; Ar = C_6H_4OMe-*p*	47% (79:21)

Scheme 5.

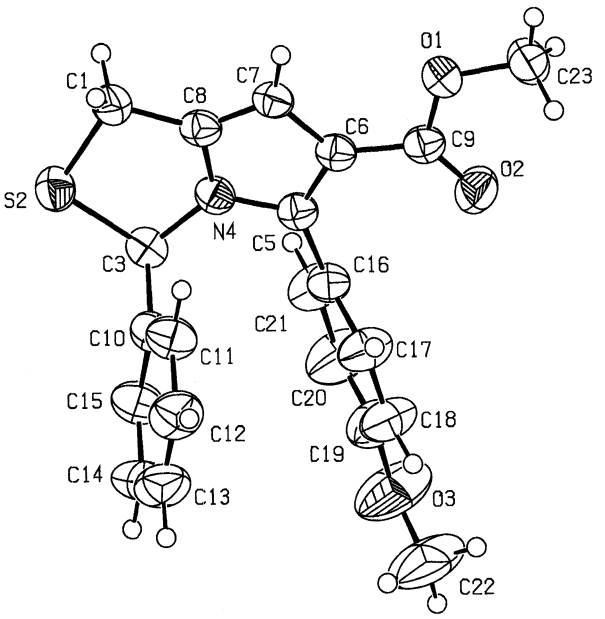


Figure 1. X-Ray crystal structure of methyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate **16c**.

The ^{1}H NMR spectrum of methyl (3*R*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate **16a** also shows the H-3 proton coupled with one of the H-1a/H-1b protons. Supported by ^{1}H–^{1}H COSY spectrum, we could also conclude that the H-7 proton is coupled with both H-1a/H-1b protons. The same coupling pattern is observed in the ^{1}H NMR spectra of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **16b**, **16c** and **16d**. In the ^{1}H NMR spectra of compounds **17a**–**17d** only the coupling between the H-3 proton with one of the H-1a/H-1b protons could be observed. This ^{1}H NMR data is consistent with the assigned regiochemistry.

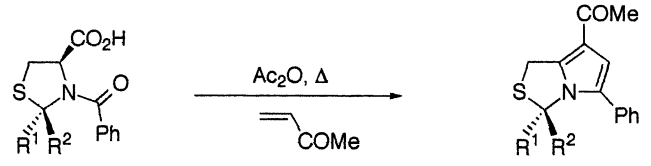
The structural assignment of compound **16c** was also supported by a NOESY spectrum. The absence of cross peaks between H-7 and the aromatic protons of the *p*-methoxyphenyl group and the observed cross peaks between these aromatic protons and the methyl ester group indicate that we are in the presence of a 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative bearing a carboxylate group at C-6.

This observation was corroborated by the X-ray structure determination of compound **16c** (Fig. 1). The absolute configuration of the molecule was established from the X-ray diffraction data using Flack's method[6] which unambiguously assigns the *R* configuration to the chiral centre C-3 (Flack's parameter refined to η=0.011(18); should be 0 for the correct, 1 for the inverted structure). The pyrrole ring is planar with a rms deviation of only 0.0025 Å from the least squares plane. The thiazolidine ring has a twisted conformation with a local pseudo two-fold axis running through S2 and the middle of the C-8/N-4 bond. The two-fold asymmetry[7] parameter ΔC_2[C-8/N-4] is 0.4(2)°. The ring puckering parameters[8] q_2 and ϕ_2 are 0.111(2) Å and 88.1(11)°, respectively. The phase angle of the pure twisted conformation is 90°. C-8 and N-4 are on opposite sides of the plane passing through S-2, C-1 and C-3 at distances −0.079(4) and 0.095(5) Å, respectively. The dihedral angle between the two phenyl rings is 26.4(2)°. The structure features no classical hydrogen bonds.

Coppola et al. have previously reported that cycloadditions of methyl propiolate with bicyclic mesoionic compounds with single-tethered substituents is characterised by a regioselectivity where the β-carbon of the propiolate combines preferentially with the untethered centre.[9] This was attributed to the ability of the untethered centre of the münchnone to became more pyramidalised in the transition state thereby allowing for a greater degree of bond formation with the β-carbon of the propiolate. Our own observations indicate that (5*R*)-3-methyl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate reacts with methyl propiolate giving exclusively one regioisomer with the same regioselectivity.[3b]

In contrast with these facts, the dipolar cycloaddition of (5*R*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates (**9a** and **9c**) and (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates (**9b** and **9d**) with methyl propiolate led to the formation of the two possible regioisomers being the major product the result of a regioselectivity where β-carbon of the propiolate combines with the tethered centre. These bicyclic münchnones are characterised by having an aryl group at the untethered centre and this can prevent the pyramidalised of this centre in the transition state thus explaining the observed regioselectivity.

In fact the regiochemistry involved in the cycloaddition of the mesoionic compounds **9a**–**9d** with methyl propiolate is similar to the one observed in the cycloaddition of this dipolarophile with monocyclic münchnones which also gives rise to a mixture of pyrrole regioisomers, the major product resulting from an interaction where the carbonyl-substituted terminus of the münchnone combines with the β-carbon of methyl propiolate.[9]

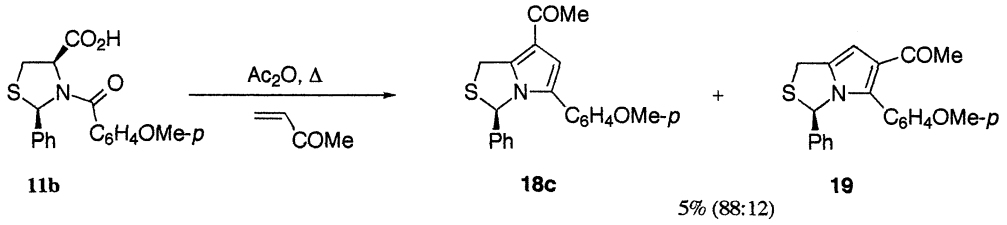


18

11a R^1 = H; R^2 = Ph
14a R^1 = Ph; R^2 = H

18a R^1 = H; R^2 = Ph 37%
18b R^1 = Ph; R^2 = H 24%

Scheme 6.



Scheme 7.

The presence of the *p*-methoxy group in the mesoionic aryl substituent at C-3 leads to higher regioselectivity (Scheme 5). The effect of this group on the selectivity can be attributed to the reduced pyramidalisation of the C-3 dipole terminus in the transition state due to the contribution from the quinoid resonance form.

The cycloaddition of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **9a**–**9ab** with methyl vinyl ketone was also performed (Scheme 6). From the reaction of (5*R*)-3,5-diphenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate (**9a**) and (5*S*)-3,5-diphenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate (**9b**) only one regioisomer was obtained in each case: chiral (3*R*)-7-acetyl-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18a** was isolated in 37% yield and (3*S*)-7-acetyl-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18b** in 24% yield.

The cycloaddition of (5*R*)-3-(*p*-methoxybenzoyl)-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate (**9c**) with methyl vinyl ketone led to a 88:12 mixture of regioisomers (3*R*)-7-acetyl-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18c** and (3*R*)-6-acetyl-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative **19** in 5% yield (Scheme 7).

Based on a comparison of the ^{1}H NMR spectra of compounds **18a**–**18c** and **19** with those of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **16a**–**16d** and **17a**–**17d** we could determine the structure of the acetyl derivatives (Table 1). The ^{1}H NMR spectra of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives bearing a carboxylate or an acetyl group at C-6 are characterised by having the H-3 and H-1 resonances at a lower chemical shift then the ones observed for the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles with a carboxylate or an acetyl group at C-6.

The structural assignment of compound **18c** was also based on a NOESY spectrum. Cross peaks were observed between H-6 and the aromatic protons of the *p*-methoxyphenyl group. On the other hand, no cross peaks were observed between the methyl ester group and the aromatic protons of the *p*-methoxyphenyl group. This suggests that compound **18c** is the regioisomer with the acetyl group at C-7.

Table 1. Selected chemical shifts for 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **16a**–**16d**, **17a**–**17d**, **18a**–**18c** and **19**

	δ (ppm)				δ (ppm)		
	H-1a and H-1b	H-3	H-7		H-1a and H-1b	H-3	H-6
16a	4.12 and 4.36	6.21	6.50	**17a**	4.41 and 4.54	6.54	6.75
16b	4.12 and 4.36	6.21	6.50	**17b**	4.42 and 4.55	6.54	6.76
16c	4.10 and 4.35	6.19	6.48	**17c**	4.40 and 4.53	6.46	6.67
16d	4.10 and 4.35	6.19	6.48	**17d**			
				18a	4.45 and 4.58	6.52	6.66
				18b	4.43 and 4.56	6.50	6.67
19	4.10 and 4.36	6.07	6.51	**18c**	4.44 and 4.56	6.44	6.60

The results obtained from the dipolar cycloaddition of münchnones **9a**–**9d** with methyl vinyl ketone and methyl propiolate suggest that stereoelectronic transition state interactions between the substituents of the münchnone and the substituents of the dipolarophile play an important role in determining the regioselectivity. This observation is in agreement with the work of Gribble et al. on the 1,3-dipolar cycloaddition of unsymmetrical münchnones with 2- and 3-nitroindoles.[10]

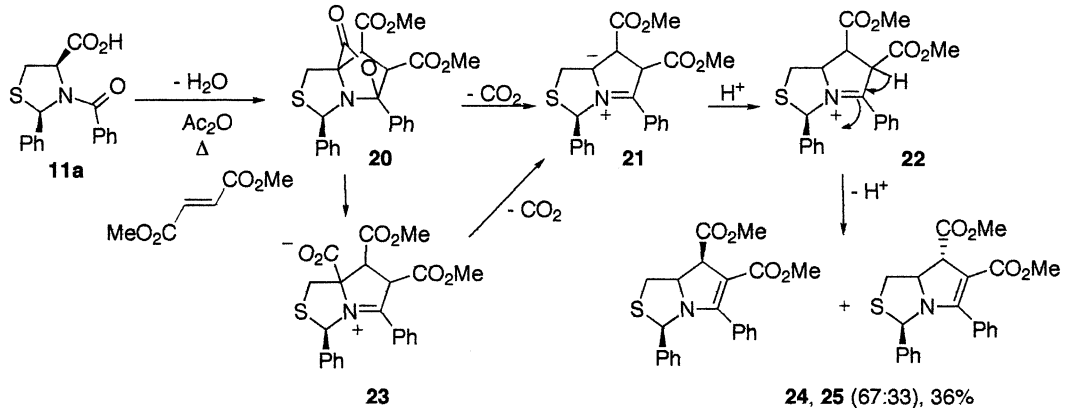
(2*R*,4*R*)-*N*-Benzoyl-2-phenylthiazolidine-4-carboxylic acid **11a** was heated in acetic anhydride in the presence of dimethyl fumarate giving a 67:33 mixture of diastereoisomers (**24** and **25**) in 36% yield (Scheme 8). Based on the ^{1}H NMR spectrum we could determine the structure of these compounds as being 3,5-diphenyl-7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates. This result shows that the initially formed dipolar cycloadduct does not lead to the aromatisation to the pyrrole ring. The synthesis of compounds **24** and **25** can be rationalised as described in Scheme 8. We have previously reported that the cycloaddition of (5*R*)-3-methyl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]-oxazol-4-ium-1-olate with acrylonitrile leads to 5,6-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives.[3b] In the present case 7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives were obtained as a consequence of a different substitution pattern of the azomethine ylide intermediate.

3. Conclusion

The intermolecular 1,3-dipolar cycloaddition of (5*R*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates (**9a** and **9c**) and (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo-[3,4-*c*]oxazol-4-ium-1-olates (**9b** and **9d**) is described.

The cycloaddition with dimethyl acetylenedicarboxylate led to the synthesis of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles in very high yield. These reactions proved to be more efficient than the previously reported cycloaddition of (5*R*)-3-methyl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate.[3b]

Cycloadditions with other dipolarophiles led to 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles in similar yields to the ones obtained with (5*R*)-3-methyl-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate although in some cases different regioselectivity was observed. From the reaction of münchnones



Scheme 8.

9a–**9d** with methyl propiolate the regioisomers 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate and 1*H*,3*H*-pyrrolo-[1,2-*c*]thiazole-7-carboxylate derivatives were obtained in each case. The cycloadditions of münchnones **9a** and **9b** with methyl vinyl ketone were completely regioselective (100:0) whereas with **9c** both regioisomers were obtained (88:12).

The study allowed to broaden the scope of this cycloaddition strategy to chiral pyrrolo[1,2-*c*]thiazoles, a class of compounds with potential biological activity.[2] New chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles with *R* configuration (**15a**, **15c**, **16a**, **16c**, **17a**, **17c**, **18a**, **18c** and **19**) and with *S* configuration (**15b**, **15d**, **16b**, **16d**, **17b**, **17d** and **18b**) were obtained. The synthesis of 7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates (**24** and **25**) was also achieved.

4. Experimental

^{1}H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz or on a Varian Unity-500 instrument operating at 500 MHz where indicated. ^{13}C spectra were recorded on a Varian Unity-500 instrument operating at 125 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Mass spectra were recorded under electron impact at 70 eV on a VG Micromass 7070E instrument. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Mp were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Methyl 2-phenylthiazolidine-4-carboxylate **12** and 2-phenylthiazolidine-4-carboxylic acid **10** were prepared using the general procedure described in the literature and were isolated as mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers.[11] In the case of thiazolidine **10** the compound precipitates from the reaction mixture and was isolated by filtration.

4.1. General procedure for the synthesis of (2*R*,4*R*)-*N*-acyl-2-phenylthiazolidine-4-carboxylic acids and esters

To a stirred solution of the thiazolidine (29.1 mmol) in THF (60 mL), triethylamine (72.2 mmol) was added dropwise at −10°C. After 15 min at room temperature the solution was evaporated. The triethylamine salt was dissolved in THF (90 mL) and the solution was cooled at −10°C. The acid chloride (34.9 mmol) was added dropwise and after stirring at room temperature for 1 h the solvent was evaporated off. The residue was treated with water (150 mL) and then with 25% HCl to pH 3 and extracted with ethyl acetate. The organic layer was washed with water, separated and dried over magnesium sulphate and the solvent evaporated off.

4.1.1. (2*R*,4*R*)-*N*-Benzoyl-2-phenylthiazolidine-4-carboxylic acid 11a. (76%). Mp 153.6–155.3°C (from ethyl ether–hexane). (Found: C, 65.2; H, 4.9; N, 4.3; S, 10.4. $C_{17}H_{15}NO_3S$ requires C, 65.2; H, 4.8; N, 4.5; S, 10.2%). δ_H (run at 50°C) 3.37 (1H, dd, *J*=12.3 and 7.0 Hz, SCH_2–), 3.54 (1H, dd, *J*=12.3 and 7.0 Hz, SCH_2–), 5.19 (1H, approx. t, *J*=7.0 Hz, –CHCOOH), 6.17 (1H, s, –C*H*Ph) and 7.19–7.40 (10H, m, Ar-H); *m*/*z* 313 (M^+, 0.1%), 241 (25), 105 (100), 77 (54). $[\alpha]_D^{25}$=+147 (*c*=0.1, CH_2Cl_2).

4.1.2. (2*R*,4*R*)-*N*-(*p*-Methoxybenzoyl)-2-phenylthiazolidine-4-carboxylic acid 11b. (50%). Compound **11b** was isolated as foam (Found: C, 62.5; H, 5.0; N, 3.6. $C_{18}H_{17}NO_4S$ requires C, 63.0; H, 5.0; N, 4.1%). δ_H 3.37 (1H, dd, *J*=12.3 and 7.0 Hz, SCH_2–), 3.48 (1H, dd, *J*=12.3 and 7.0 Hz, SCH_2–), 3.78 (3H, s), 5.20 (1H, approx. t, *J*=7.0 Hz, –CHCOOH), 6.23 (1H, s, –C*H*Ph), 6.76–6.79 (2H, d, Ar-H, *J*=9.0 Hz) and 7.27–7.38 (7H, m, Ar-H); *m*/*z* 343 (M^+, 0.1%), 271 (16), 135 (100) and 77 (15).

4.1.3. Methyl (2*R*,4*R*)-*N*-benzoyl-2-phenylthiazolidine-4-carboxylate 13. (84%). Mp 72.2–73.7°C (from ethyl ether–hexane). (Found: C, 65.7; H, 5.3; N, 4.1. $C_{18}H_{17}NO_3S$ requires C, 66.0; H, 5.2; N, 4.3%). ^{1}H NMR spectrum at room temperature gives very broad lines; *m*/*z* 327 (M^+, 1%), 268 (5), 241 (61), 222 (9), 105 (100) and 77 (32).

4.2. Synthesis of (2*R*,4*R*)-*N*-benzoyl-2-phenylthiazolidine-4-carboxylic acid 11a from methyl (2*R*,4*R*)-*N*-benzoyl-2-phenylthiazolidine-4-carboxylate 13

The methyl *N*-acyl-2-phenylthiazolidine-4-carboxylate (1 mmol) and LiI (4 mmol) were dissolved in ethyl acetate (1.3 mL). The reaction mixture was protected from light and heated at reflux for 6 h. Water was added (5 mL) and the solution was acidified with HCl 1 M and extracted with

ethyl acetate. The organic phase was washed with water and with saturated aqueous solution of NaCl. The organic solvent was evaporated off. To the residue a saturated aqueous solution of $NaHCO_3$ was added and the solution was washed with DCM. The aqueous solution was acidified with concentrated HCl and extracted with ethyl acetate. The organic phase was dried and the solvent was evaporated off giving (2*R*,4*R*)-*N*-benzoyl-2-phenylthiazolidine-4-carboxylic acid **11a** in 74% yield. The product was identified by comparison with the specimen previously prepared.

4.3. General procedure for the synthesis of (2*S*,4*R*)-*N*-acyl-2-phenylthiazolidine-4-carboxylic acids

To a stirred solution of the thiazolidine (4.88 mmol) in dry pyridine (12 mL), the acid chloride (9.75 mmol) was added dropwise at −10°C. After 4 h at 0°C, the solution was treated with water (20 mL) at room temperature and then with 25% HCl to pH 3 and extracted with ethyl acetate. The organic layer was washed with water, separated and dried over magnesium sulphate and the solvent evaporated off.

4.3.1. (2*S*,4*R*)-*N*-Benzoyl-2-phenylthiazolidine-4-carboxylic acid 14a. (44%). Compound **11b** was isolated as a foam. (Found: C, 65.0; H, 5.0; N, 4.8. $C_{17}H_{15}NO_3S$ requires C, 65.2; H, 4.8; N, 4.5%). ^{1}H NMR spectrum at room temperature gives very broad lines; *m*/*z* 313 (M^+, 0.1%), 268 (0.5), 251 (0.6); 241 (62), 105 (100) and 77 (70). $[\alpha]_D^{25}=-146$ (*c*=0.1, CH_2Cl_2).

4.3.2. (2*S*,4*R*)-*N*-(*p*-Methoxybenzoyl)-2-phenylthiazolidine-4-carboxylic acid 14b. (75%, d.e. 50%). Compound **14b** was isolated as a foam. Pure (2*S*,4*R*)-isomer was isolated by flash chromatography (25%). (Found: C, 62.3; H, 5.0; N, 3.9; S, 9.0. $C_{18}H_{17}NO_4S$ requires C, 63.0; H, 5.0; N, 4.1; S, 9.3%). ^{1}H NMR spectrum at room temperature gives very broad lines.

4.4. General procedure for the synthesis of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles

N-Acyl-2-phenylthiazolidine-4-carboxylic acid (5 mmol), dipolarophile (7.5 mmol) and Ac_2O (20 mL) were heated at reflux for 4 h. The reaction was cooled to room temperature and was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous solution of $NaHCO_3$ and with water, dried ($MgSO_4$) and evaporated off. The crude product was purified by flash chromatography [hexane–ethyl acetate (3:1), hexane–ethyl acetate (2:1) then hexane–ethyl acetate (1:1)].

4.4.1. Dimethyl (3*R*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6,7-dicarboxylate 15a. The titled compound was prepared by the general procedure from thiazolidine **11a** using dimethylacetylene dicarboxylate as dipolarophile (90%). Compound **15a** was isolated as an oil. δ_H 3.66 (3H, s), 3.87 (3H, s), 4.43 (1H, d, *J*=15.1 Hz, SCH_2–), 4.57 (1H, dd, *J*=15.1 and 1.7 Hz, SCH_2–), 6.32 (1H, d, *J*=1.7 Hz, –*CH*Ph), 6.69–6.73 (2H, m, Ar-H), 7.02–7.05 (2H, m, Ar-H) and 7.09–7.22 (6H, m, Ar-H); *m*/*z* 393 (M^+, 48%), 361 (64), 272 (73), 240 (47), 121 (100) and 77 (22); Accurate mass: 393.10375. $C_{22}H_{19}NO_4S$ requires 393.10349. $[\alpha]_D^{25}=+201$ (*c*=0.1, CH_2Cl_2).

4.4.2. Dimethyl (3*S*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6,7-dicarboxylate 15b. The titled compound was prepared by the general procedure from thiazolidine **11a** using dimethylacetylene dicarboxylate as dipolarophile (83%). Compound **15b** was isolated as an oil. δ_H 3.65 (3H, s), 3.86 (3H, s), 4.42 (1H, d, *J*=15.1 Hz, SCH_2–), 4.57 (1H, dd, *J*=15.1 and 1.7 Hz, SCH_2–), 6.32 (1H, d, *J*=1.7 Hz, –*CH*Ph), 6.71–6.74 (2H, m, Ar-H) and 7.01–7.21 (8H, m, Ar-H); *m*/*z* 393 (M^+, 53%), 361 (79), 272 (99), 121 (100) and 77 (46). $[\alpha]_D^{25}=-209$ (*c*=0.1, CH_2Cl_2).

4.4.3. Dimethyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 15c. The titled compound was prepared by the general procedure from thiazolidine **11b** using dimethylacetylene dicarboxylate as dipolarophile (85%). Mp 94.7–96.4°C (from ethyl ether–hexane). (Found: C, 65.0; H, 5.1; N, 3.2; S, 7.4. $C_{23}H_{21}NO_5S$ requires C, 65.2; H, 5.0; N, 3.3; S, 7.6%). δ_H 3.67 (3H, s), 3.75 (3H, s), 3.86 (3H, s), 4.41 (1H, d, *J*=15.1 Hz, SCH_2–), 4.56 (1H, dd, *J*=15.1 and 1.4 Hz, SCH_2–), 6.28 (1H, d, *J*=1.4 Hz, –*CH*Ph), 6.69 (2H, d, *J*=8.5 Hz, Ar-H), 6.72–6.79 (2H, m, Ar-H), 6.96 (2H, d, *J*=8.5 Hz, Ar-H) and 7.11–7.16 (3H, m, Ar-H); *m*/*z* 423 (M^+, 89%), 341 (22), 301 (100); 281 (61), 207 (97) and 73 (33). $[\alpha]_D^{25}=+230$ (*c*=1, CH_2Cl_2).

4.4.4. Dimethyl (3*S*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 15d. The titled compound was prepared by the general procedure from thiazolidine **11b** using dimethylacetylene dicarboxylate as dipolarophile (92%). Mp 91.8–93.6°C. (Found C, 64.8; H, 5.0; N, 3.2; S, 7.8. $C_{23}H_{21}NO_5S$ requires C, 65.2; H, 5.0; N, 3.3; S, 7.6%). δ_H 3.67 (3H, s), 3.75 (3H, s), 3.86 (3H, s), 4.42 (1H, d, *J*=15.1 Hz, SCH_2–), 4.56 (1H, dd, *J*=15.1 and 1.6 Hz, SCH_2–), 6.28 (1H, d, *J*=1.6 Hz, –*CH*Ph), 6.69 (2H, d, *J*=8.8 Hz, Ar-H), 6.73–6.76 (2H, m, Ar-H), 6.95 (2H, d, *J*=8.8 Hz, Ar-H) and 7.14–7.17 (3H, m, Ar-H); *m*/*z* 423 (M^+, 93%), 301 (100), 286 (60), 207 (25), 185 (18), 135 (15) and 77 (10). $[\alpha]_D^{25}=-224$ (*c*=1, CH_2Cl_2).

4.4.5. Methyl (3*R*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6-carboxylate 16a and methyl (3*R*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylate 17a. The titled compounds were prepared by the general procedure from thiazolidine **11a** using methyl propiolate as dipolarophile (68%). The crude product was purified by flash chromatography giving a 62:38 mixture of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles: **16a** δ_H 3.64 (3H, s), 4.12 (1H, dd, *J*=13.3 and 0.9 Hz, SCH_2–), 4.36 (1H, approx. dt, *J*=13.3 and 1.1 Hz, SCH_2–), 6.21 (1H, d, *J*=0.9 Hz, –*CH*Ph), 6.50 (1H, approx. t, *J*=1.1 Hz), 6.69–6.73 (2H, m, Ar-H), 7.01–7.04 (2H, m, Ar-H) and 7.10–7.22 (6H, m, Ar-H); **17a** 3.86 (3H, s), 4.41 (1H, d, *J*=15.0 Hz, SCH_2–), 4.54 (1H, dd, *J*=15.0 and 1.5 Hz, SCH_2–), 6.54 (1H, bs), 6.75 (1H, s), 6.78–6.79 (2H, m, Ar-H) and 6.01–6.18 (8H, m, Ar-H); GC–MS: **16a** *m*/*z* 335 (M^+, 70%), 214 (100), 198 (53), 182 (14) and 121 (22); **17a** *m*/*z* 335 (M^+, 81%), 320 (25), 214 (100), 182 (14), 155 (18) and 121 (31).

The major component (**16a**) is separated by selective crystallisation (ethyl ether–hexane).

16a: mp 125.8–127.3°C. (Found: C, 71.7; H, 5.2; N, 4.3. $C_{20}H_{17}NO_2S$ requires C, 71.6; H, 5.1; N, 4.2%). δ_H 3.64 (3H, s), 4.12 (1H, dd, J=13.3 and 0.9 Hz, SCH_2–), 4.36 (1H, approx. dt, J=13.3 and 1.1 Hz, SCH_2–), 6.21 (1H, d, J=0.9 Hz, –*CH*Ph), 6.50 (1H, approx. t, J=1.1 Hz), 6.69–6.73 (2H, m, Ar-H), 7.01–7.04 (2H, m, Ar-H) and 7.10–7.22 (6H, m, Ar-H) [the assignment was based on a COSY (^{1}H,^{1}H) spectrum]; *m/z* 335 (M^+, 41%), 214 (100), 198 (51) and 121 (31). $[\alpha]_D^{25}$=+348 (c=0.1, CH_2Cl_2).

4.4.6. Methyl (3*S*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6-carboxylate 16b and methyl (3*S*)-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylate 17b. The titled compounds were prepared by the general procedure from thiazolidine **14a** using methyl propiolate as dipolarophile (55%). The crude product was purified by flash chromatography giving a 64:36 mixture of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles: **16b** δ_H 3.65 (3H, s), 4.12 (1H, dd, J=13.3 and 1.0 Hz, SCH_2–), 4.36 (1H, approx. dt, J=13.3 and 1.1 Hz, SCH_2–), 6.21 (1H, d, J=0.9 Hz, –*CH*Ph), 6.50 (1H, approx. t, J=1.1 Hz), 6.69–6.72 (2H, m, Ar-H), 7.01–7.05 (2H, m, Ar-H), 7.11–7.20 (6H, m, Ar-H); **17b** δ_H 3.87 (3H, s), 4.42 (1H, d, J=15.1 Hz, SCH_2–), 4.55 (1H, dd, J=15.1 and 1.6 Hz, SCH_2–), 6.54 (1H, d, J=1.6 Hz, –*CH*Ph), 6.76 (1H, s), 6.77–6.81 (2H, m, Ar-H), 7.12–7.20 (8H, m, Ar-H); GC–MS: **16b** *m/z* 335 (M^+, 53%), 283 (19), 214 (100), 198 (58) and 121 (31); **17b** *m/z* 335 (M^+, 81%), 320 (25), 214 (100), 155 (18) and 121 (31).

The major component (**16b**) is separated by selective crystallisation (ethyl ether–hexane).

16b: mp 118–119.6°C. (Found: C, 71.9; H, 4.8; N, 3.8. $C_{20}H_{17}NO_2S$ requires C, 71.6; H, 5.1; N, 4.2%). δ_H 3.65 (3H, s), 4.12 (1H, dd, J=13.3 and 1.0 Hz, SCH_2–), 4.36 (1H, approx. dt, J=13.3 and 1.1 Hz, SCH_2–), 6.21 (1H, d, J=0.9 Hz, –*CH*Ph), 6.50 (1H, approx. t, J=1.1 Hz), 6.69–6.72 (2H, m, Ar-H), 7.01–7.05 (2H, m, Ar-H), 7.11–7.20 (6H, m, Ar-H); *m/z* 335 (M^+, 53%), 283 (19), 214 (100), 198 (58) and 121 (31). $[\alpha]_D^{25}$=−310 (c=0.1, CH_2Cl_2).

4.4.7. Methyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate 16c and methyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-7-carboxylate 17c. The titled compounds were prepared by the general procedure from thiazolidine **11b** using methyl propiolate as dipolarophile (55%). The crude product was purified by flash chromatography giving a 70:30 mixture of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles: **16c** δ_H 3.66 (3H, s), 3.76 (3H, s), 4.10 (1H, dd, J=13.3 and 0.7 Hz, SCH_2–), 4.35 (1H, approx. d, J=13.3 Hz, SCH_2–), 6.19 (1H, bs, –*CH*Ph), 6.48 (1H, bs), 6.70 (2H, d, J=8.7 Hz, Ar-H), 6.69–6.75 (2H, m, Ar-H), 6.95 (2H, d, J=8.7 Hz, Ar-H), 7.13–7.16 (3H, m, Ar-H); **17c** δ_H 3.74 (3H, s), 3.86 (3H, s), 4.40 (1H, d, J=15.0 Hz, SCH_2–), 4.53 (1H, dd, J=15.0 and 1.6 Hz, SCH_2–), 6.46 (1H, d, J=1.6 Hz, –*CH*Ph), 6.67 (1H, s), 6.71 (2H, d, J=8.8 Hz, Ar-H), 6.78–6.81 (2H, m, Ar-H), 7.04 (2H, d, J=8.8 Hz, Ar-H), 7.14–7.119 (3H, m, Ar-H); GC–MS: **16c** *m/z* 365 (M^+, 57%), 243 (78), 228 (100), 212 (9), 121 (10) and 77 (4): **17c** *m/z* 365 (M^+, 58%), 243 (100), 228 (10), 185 (11), 134 (10), 121 (8) and 77 (3).

The major component (**16c**) is separated by selective crystallisation (ethyl ether–hexane).

17c: mp 135–137°C (from ethyl ether). (Found: C, 69.2; H, 5.4; N, 3.70; S, 9.2%. $C_{21}H_{19}NO_3S$ requires C, 69.0; H, 5.2; N, 3.8; S, 8.8%). δ_H 3.66 (3H, s), 3.76 (3H, s), 4.10 (1H, dd, J=13.3 and 0.7 Hz, SCH_2–), 4.35 (1H, approx. d, J=13.3 Hz, SCH_2–), 6.19 (1H, bs, –*CH*Ph), 6.48 (1H, bs), 6.70 (2H, d, J=8.7 Hz, Ar-H), 6.69–6.75 (2H, m, Ar-H), 6.95 (2H, d, J=8.7 Hz, Ar-H), 7.13–7.16 (3H, m, Ar-H); *m/z* 365 (M^+, 57%), 243 (78), 228 (100), 212 (9), 121 (10) and 77 (4). $[\alpha]_D^{25}$=+241 (c=0.1, CH_2Cl_2).

4.4.8. Methyl (3*S*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate 16d and methyl (3*S*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-7-carboxylate 17d. The titled compounds were prepared by the general procedure from thiazolidine **14b** using methyl propiolate as dipolarophile (47%). The crude product was purified by flash chromatography giving a 79:21 mixture of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles: **16d** δ_H 3.66 (3H, s), 3.76 (3H, s), 4.10 (1H, dd, J=13.3 and 1.0 Hz, SCH_2–), 4.35 (1H, approx. dt, J=13.3 and 1.0 Hz, SCH_2–), 6.19 (1H, d, J=1.0 Hz, –*CH*Ph), 6.48 (1H, approx. t, J=1.0 Hz), 6.70 (2H, d, J=8.8 Hz, Ar-H), 6.72–6.75 (2H, m, Ar-H), 6.95 (2H, d, J=8.8 Hz, Ar-H) and 7.13–7.16 (3H, m, Ar-H); **17d** δ_H 3.74 (3H, s), 3.86 (3H, s), 4.40 (1H, d, J=15.0 Hz, SCH_2–), 4.52 (1H, dd, J=15.0 and 1.5 Hz, SCH_2–), 6.46 (1H, d, J=1.5 Hz, –*CH*Ph), 6.67 (1H, s), 6.71 (2H, d, J=8.8 Hz, Ar-H), 6.68–6.80 (2H, m, Ar-H), 7.04 (2H, d, J=8.8 Hz, Ar-H), 7.12–7.18 (3H, m, Ar-H); GC–MS: **16d** *m/z* 365 (M^+, 54%), 243 (73), 228 (100), 121 (3) and 77 (3); **17d** *m/z* 365 (M^+, 57%), 243 (100), 228 (12), 121 (10) and 77 (3).

The major component (**16d**) is separated by selective crystallisation (ethyl ether–hexane).

16d: mp 110–113.5°C. (Found: C, 68.8; H, 5.2; N, 3.4; S, 8.6. $C_{21}H_{19}NO_3S$ requires C, 69.0; H, 5.2; N, 3.8; S, 8.8%). δ_H 3.66 (3H, s), 3.76 (3H, s), 4.10 (1H, dd, J=13.3 and 1.0 Hz, SCH_2–), 4.35 (1H, approx. dt, J=13.3 and 1.0 Hz, SCH_2–), 6.19 (1H, d, J=1.0 Hz, –*CH*Ph), 6.48 (1H, approx. t, J=1.0 Hz), 6.70 (2H, d, J=8.8 Hz, Ar-H), 6.72–6.75 (2H, m, Ar-H), 6.95 (2H, d, J=8.8 Hz, Ar-H) and 7.13–7.16 (3H, m, Ar-H); *m/z* 365 (M^+, 65%), 334 (5), 243 (85), 228 (100), 121 (12) and 77 (5). $[\alpha]_D^{25}$=−240 (c=0.1, CH_2Cl_2).

4.4.9. (3*R*)-7-Acetyl-3,5-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*]-thiazole 18a. The titled compound was prepared by the general procedure from thiazolidine **11a** using methyl vinyl ketone (25 mmol) as dipolarophile and the reaction time was 15 h (37%). Compound **18a** was isolated as an oil. δ_H 2.46 (3H, s), 4.45 (1H, d, J=15.4 Hz, SCH_2–), 4.58 (1H, dd, J=15.4 and 1.8 Hz, SCH_2–), 6.52 (1H, d, J=1.8 Hz, –*CH*Ph), 6.66 (1H, s), 6.77–6.81 (2H, m, Ar-H), 7.10–7.45 (7H, m, Ar-H), 7.72–7.75 (1H, m, Ar-H); *m/z* 319 (M^+, 100%), 198 (77), 121 (76) and 77 (38). $[\alpha]_D^{25}$=+143 (c=0.1, CH_2Cl_2).

4.4.10. (3*S*)-7-Acetyl-3,5-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole 18b. The titled compound was prepared by the

general procedure from thiazolidine **14a** using methyl vinyl ketone (25 mmol) as dipolarophile (24%). Compound **18b** was isolated as an oil. δ_H 2.45 (3H, s), 4.43 (1H, d, J=15.4 Hz, SCH_2–), 4.56 (1H, dd, J=15.4 and 1.8 Hz, SCH_2–), 6.50 (1H, d, J=1.8 Hz, –*CH*Ph), 6.67 (1H, s), 6.77–6.78 (2H, m, Ar-H), 7.10–7.41 (7H, m, Ar-H) and 7.70–7.73 (1H, m, Ar-H); *m*/*z* 319 (M^+, 100%), 286, (20), 198 (66), 182 (29), 121 (30) and 77 (9). $[\alpha]_D^{25}=-122$ (c=0.1, CH_2Cl_2).

4.4.11. (3*R*)-7-Acetyl-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole 18c and (3*R*)-6-acetyl-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole 19. The titled compounds were prepared by the general procedure from thiazolidine **11b** using methyl vinyl ketone (25 mmol) as dipolarophile and the reaction time was 15 h (5%). The crude product was purified by flash chromatography giving a 88:12 mixture of 1*H*,3*H*-pyrrolo[1,2-*c*]-thiazoles **18c** and **19** and was isolated as an oil: **18c**: δ_H (500 MHz) 2.45 (3H, s), 3.75 (3H, s), 4.44 (1H, d, J=15.4 Hz, SCH_2–), 4.56 (1H, dd, J=15.4 and 1.7 Hz, SCH_2–), 6.44 (1H, d, J=1.7 Hz, –C*H*Ph), 6.60 (1H, s), 6.69–6.75 (2H, m, Ar-H), 6.78–6.80 (2H, m, Ar-H), 7.03 (2H, d, J=8.8 Hz, Ar-H), 7.15–7.17 (3H, m, Ar-H); δ_C (125 MHz) 27.6, 30.5, 55.2, 65.1, 112.9, 113.8, 125.3, 125.5, 128.4, 128.6, 128.8, 129.3, 131.5, 141.2, 141.3, 159.1, 193.9; **19**: δ_H (500 MHz) 2.22 (3H, s), 3.76 (3H, s), 4.10 (1H, dd, J=13.4 and 0.9 Hz, SCH_2–), 4.36 (1H, bd, J=13.4 Hz, SCH_2–), 6.07 (1H, bs, –C*H*Ph), 6.51 (1H, bs), 6.69–6.75 (4H, m, Ar-H), 6.88 (2H, d, J=8.4 Hz, Ar-H), 7.15–7.17 (3H, m, Ar-H); GC–MS: **18c**: *m*/*z* 349 (M^+, 62%), 282 (5), 227 (100), 212 (30), 121 (10) and 77 (6); **19** *m*/*z* 349 (M^+, 60%), 281 (62), 227 (100), 207 (92), 147 (20) and 73 (48).

4.4.12. Dimethyl (3*R*,7*R*)-3,5-diphenyl-7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]tiazole-6,7-dicarboxylate and dimethyl (3*R*,7*S*)-3,5-diphenyl-7,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-tiazole-6,7-dicarboxylate 24 and 25. The titled compounds were prepared by the general procedure from thiazolidine **11a** using dimethyl fumarate as dipolarophile, the reaction time was 15 h and was isolated as a mixture of diastereoisomers (67:33) in 36% yield (isolated as an oil). *Major component*: δ_H 3.08 (1H, dd, J=10.6 and 8.4 Hz, SCH_2–), 3.26 (1H, dd, J=10.6 and 6.9 Hz, SCH_2–), 3.56 (3H, s), 3.78 (3H, s), 3.90 (1H, d, J=2.5 Hz, –*CH*CO_2CH_3), 4.26–4.37 (1H, m, –CH_2*CH*–) and 7.28–7.40 (10H, m, Ar-H); *m*/*z* 395 (M^+, 58%), 349 (100), 336 (81), 316 (47), 214 (52), 182 (36), 121 (25), 91 (15), 78 (10) and 59 (13). *Minor component*: δ_H 2.88 (1H, dd, J=10.7 and 6.0 Hz, SCH_2–), 3.34 (1H, dd, J=10.7 and 9.1 Hz, SCH_2–), 3.52 (3H, s), 3.79 (3H, s), 4.20 (1H, d, J=1.7 Hz, –*CH*CO_2CH_3), 4.52–4.62 (1H, m, –CH_2*CH*–) and 7.28–7.40 (10H, m, Ar-H); *m*/*z* 395 (M^+, 43%), 336 (100), 325 (12), 214 (46), 182 (31), 156 (15), 121 (14), 91 (12) and 77 (12).

4.5. Crystal data for methyl (3*R*)-3-phenyl-5-(*p*-methoxyphenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxylate 16c

$C_{21}H_{19}NO_3S$. M=365.44, monoclinic, space group $P2_1$ (#4), a=6.2746(8), b=8.9708(10), c=16.8412(19) Å, β=97.93(10)° V=938.90(19) Å^3, Z=2, D_c=1.293 g cm^{-3}, F_{000}=384, μ=1.695 mm^{-1}, T=296 K. Number of independent intensities 1965 from colourless, transparent prism, 0.35×0.40×0.25 mm^3. Empirical absorption correction applied based on 9 ψ-scans, T_{min}=0.696, T_{max}=0.977, T_{ave}=0.836. No significant crystal decay was detected. Structure solution by direct methods using SHELXS97.[12] R=0.0286 for 1950 reflections with $I>2\sigma$, R_w=0.0781 for 1965 reflections used in the refinement and 238 refined parameters. H-atoms were placed at calculated positions and refined as riding on their parent atoms. X-Ray measurements were performed on a Enraf-Nonius MACH3 diffractometer[13] using Cu Kα radiation (λ=1.54184 Å) and $\omega-2\theta$ scans up to 72.03°.

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