Generation and Reactivity of 3-Carbethoxy-5-phenyl-*5H*,*7H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate

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3-Carbethoxy-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate was generated from (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid and its reactivity studied. This münchnone showed low reactivity as dipole although from the reaction with dimethyl acetylenedicarboxylate the corresponding (3*R*)-3-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-5,6,7-tricarboxylate could be isolated. The thermolysis of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid in refluxing acetic anhydride led to the synthesis of *N*-(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine. The structure of methyl (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylate was determined by X-ray crystallography.

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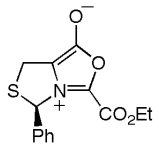
Introduction.

The study of 1,3-dipolar cycloaddition of münchnones is a topic of our current research [1]. The main objective is to broaden the scope of the intramolecular and intermolecular 1,3-dipolar cycloaddition reaction of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate derivatives in order to achieve the synthesis of a range of new chiral pyrrolo[1,2-*c*]thiazole derivatives and analogues, compounds with potential biological activity [2].

In the previous described intermolecular 1,3-dipolar cycloadditions, münchnones bearing an aryl group or methyl group at C-3, acted as masked azomethine ylides on reacting with electron deficient dipolarophiles [1c,1d].

We decided to explore the possibility of generating a 5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate bearing an electron withdrawing group at C-3 (**1**) in order to study its reactivity towards dipolarophiles.



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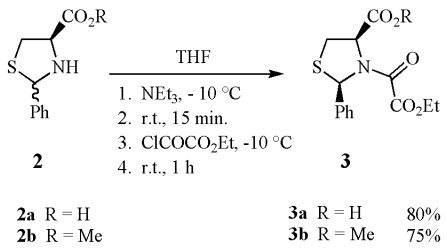
Results and Discussion.

The synthetic strategy for the generation of 5-substituted-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates involves the cyclodehydration of *N*-acyl-2-phenyl-1,3-thiazolidine-4-carboxylic acids. Thus, our first objective was to prepare (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid (**3a**). Using 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 [3c], the *cis* derivative **3a** (80%) was obtained selectively by treating with ethyl oxalylchloride the triethylamine salt of thiazolidine **2a** in tetrahydrofuran (Scheme 1).

Scheme 1



Methyl (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenyl-thiazolidine-4-carboxylate **3b** was also prepared in 75% yield from the reaction of methyl 2-phenyl-1,3-thiazolidine-4-carboxylate **2b** with ethyl oxalylchloride (Scheme 1). The ^{1}H NMR spectrum, recorded at room temperature, showed the existence of two separate rotamers. The spectrum is simplified at higher temperature as observed with other *N*-acylthiazolidines [1a,1c,1d]. We found that the proton attached to C4 appears as two singlets when the ^{1}H NMR spectrum of **3b** is recorded at room temperature, and it becomes one singlet when the spectrum is recorded at 70 ºC (in DMSO-d_6).

The structure of **3b** was determined by X-ray crystallography (Figure 1). The absolute configuration of the molecule was established from X-ray crystallography using Flack's method [4] which unambiguously assigns the *R*,*R* configuration to the two chiral centers C2 and C4 (Flack's

parameter refined to $\eta = 0.01(4)$; should be 0 for the correct, 1 for the inverted structure).

The thiazolidine ring has a twisted conformation with a local pseudo two-fold axis running through N3 and the middle of the S1-C5 bond. The two-fold asymmetry [5] parameter ΔC_2[S1-C5] is 5.02(10)°. The ring puckering parameters [6] q_2 and ϕ_2 are 0.508(1) Å, 347.2(1)°, respectively. The phase angle of the pure twisted conformation is 342°. S1 and C5 are on opposite sides of the plane passing through C2, N3 and C4 at 0.565(3) Å and -0.305(3) Å, respectively. The exocyclic angles around N3 show some asymmetry. However the sum of the valence angles around N3 is 359.74(8)°, indicating no significant pyramidalization of this atom. The methoxycarbonyl and oxalyl groups have bisectional and equatorial positions, respectively, with respect to the thiazolidine ring and both have unexceptional geometries. The phenyl ring has an axial position with torsion angles 88.22(8)° [C5-S1-C2-C8] and -105.06(9)° [C4-N3-C2-C8]. The thiazolidine and phenyl rings are almost perpendicular, the dihedral angle between the least-squares planes is 80.79(5)°

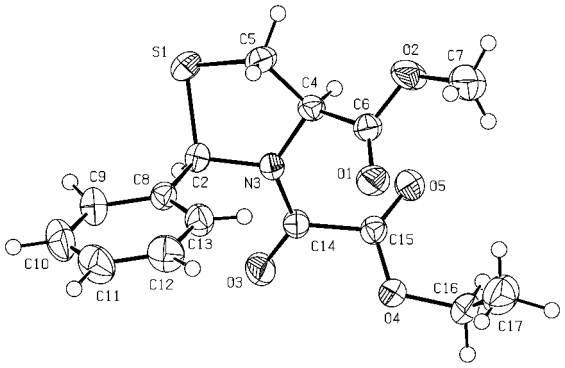
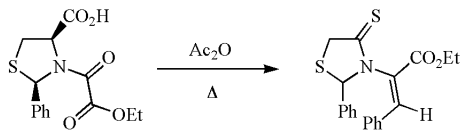


Figure 1. ORTEP plot of methyl (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylate **3b**.with anisotropic displacement ellipsoids calculated at the 50% probability level.

Ethyl 5-phenyl-*5H*,*7H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate-3-carboxylate **1** was generated, by heating at reflux a solution of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid **3a** in acetic anhydride in presence of a dipolarophile. However, the attempts to promote the 1,3-dipolar cycloaddition, using this reaction condition, with electron rich dipolarophiles (ethyl vinyl ether or dihydrofuran) and also with an electron deficient dipolarophile (dimethyl acetylenedicarboxylate) did not lead to the expected products. Although no 1,3-dipolar cycloadducts were obtained, this study led to an interesting result. From these reactions we could isolate *N*(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine (**4**) in 18% yield (Scheme 2).

Scheme 2



3a **4** 18%

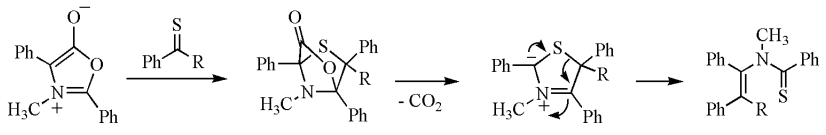
It has been reported that thiobenzophenone and methyl thiobenzoate combine with 3-methyl-2,4-diphenyloxazolium-5-olate (**5**) to give *N*-thiobenzoylenamines (**8**) and CO_2 [7]. The process involves a 1,3-dipolar cycloaddition followed by cycloreversion of carbon dioxide giving **7**. This compound undergoes a rearrangement leading to the *N*-thiobenzoylenamines **8** (Scheme 3)

The synthesis of compound **4** can be rationalized by a similar mechanistic sequence (Scheme 4). We propose the generation of thiobenzaldehyde from thiazolidine **3a** which could participate in the 1,3-dipolar cycloaddition with 3-carbethoxy-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate **1** leading to **11**. Cycloreversion of carbon dioxide followed by rearrangement allows the formation of *N*(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine **4**.

Attempts were made to make the synthesis of compound **4** more efficient. However, heating at reflux a solution of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid **3a** in acetic anhydride for 15 hours did not lead to an improvement. The reaction was also carried out in a sealed tube and a solution of **3a** in acetic anhydride was heated at 200 °C for 2 hours. From this reaction the only product that could be isolated was ethyl cinnamate **13** in 32% yield (Scheme 5).

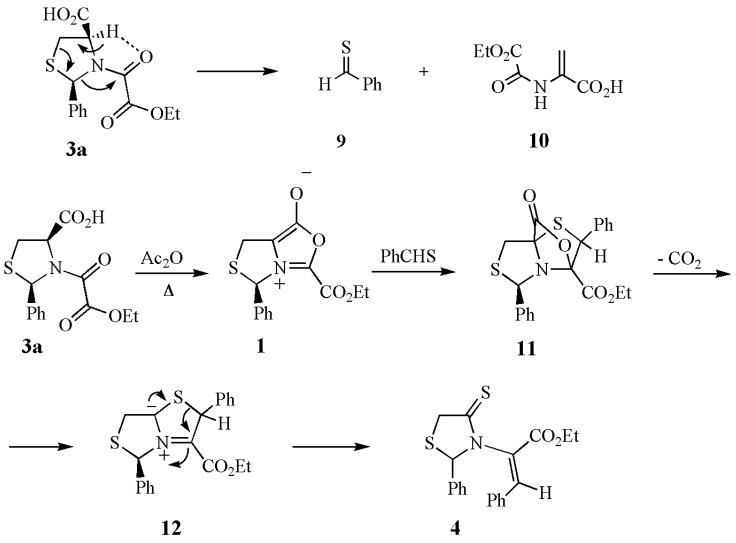
Considering that ethyl cinnamate could be the result of *N*-(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine **4** cleavage we decided to carry out the reaction of thiazolidine **3a** with acetic anhydride using milder reaction conditions. Compound **3a** was heated in acetic

Scheme 3

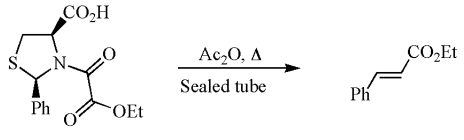


5 **6** **7** **8**

Scheme 4

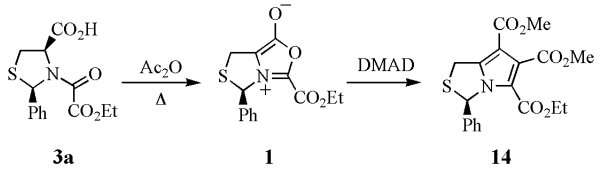


Scheme 5



anhydride at 85 °C for 2 hours. Two products could be detected by TLC one of which was compound **4**. However, only 4-thioxo-1,3-thiazolidine **4** could be isolated in low yield (3%). The very low stability of the second product indicated that it could be 3-carbethoxy-5-phenyl-5*H*,7*H*-thiazolo-[3,4-*c*]oxazol-4-ium-1-olate **1**. In fact, when the same reaction was carried out in the presence of dimethyl acetylenedicarboxylate the 1,3-dipolar cycloadduct **14** could be isolated although in low yield (Scheme 6). With ethyl vinyl ether no cycloadduct was isolated.

Scheme 6



Conclusion.

The (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid was prepared selectively from a diastereoisomeric mixture (2*S*,4*R*)- and (2*R*,4*R*)-2-phenylthiazolidine-4-carboxylic acid and used to generate 3-carbethoxy-5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olate.

This münchnone (**1**), bearing an electron withdrawing group at C-3, is less reactive towards dimethyl acetylenedicarboxylate than the derivatives bearing an aryl group or methyl group. On the other hand, münchnone **1** was not electron deficient enough to enable the dipolar cycloaddition with electron rich dipolarophiles.

The thermolysis of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid (**3a**) in acetic anhydride led to the interesting synthesis of *N*-(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine (**4**) *via* the generation of münchnone **1** as intermediate.

EXPERIMENTAL

General.

^{1}H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz. The solvent is deuteriochloroform. 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. M.p. 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 **2b** and 2-phenylthiazolidine-4-carboxylic acid **2a** 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 [8]. In the case of thiazolidine **2a** the compound precipitates from the reaction mixture and was isolated by filtration.

General Procedure for the Synthesis of (2*R*,4*R*)-*N*-Acyl-2-phenylthiazolidine-4-carboxylic Acid (**3a**) and Methyl Ester (**3b**).

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 minutes 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 hour 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.

(2*R*,4*R*)-*N*-Ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic Acid (**3a**).

This compound was obtained in 80% yield, mp 126.5-128 °C (from ethyl ether-hexane). ^{1}H nmr (two rotamers are detected): δ 0.94 and 1.34 (3H, 2xt), 3.43-3.48 (2H, m), 3.69-3.75, 3.86-3.92 and 4.29-4.33 (2H, 3xm), 5.18 and 5.53 (1H, approx. 2xt, *J* 5.5 Hz and *J* 6.3 Hz), 6.32 and 6.40 (1H, 2xs), 7.31-7.38 (3H, m, Ar-H), 7.52-7.61 (2H, m, Ar-H); m/z [the product was treated with diazomethane giving the corresponding methyl ester] 323 (M^+, 7%), 264 (11), 237 (57), 222 (100), 162 (40), 121 (53), 77 (31) and 59 (17). $[\alpha]_D^{25}$ = + 40 (c = 0.1, CH_2Cl_2).

Anal. Calcd. for $C_{14}H_{15}NO_5S$: C, 54.4; H, 4.9; N, 4.5; S, 10.4. Found: C, 54.6; H, 5.0; N, 4.4; S, 10.7.

Methyl (2*R*,4*R*)-*N*-Ethoxyoxalyl-2-phenylthiazolidine-4-carboxylate (**3b**).

This compound was obtained in 75% yield. mp 100.8-101.8 °C (from THF-ethyl ether). ^{1}H nmr (two rotamers are detected): δ 0.93 and 1.35 (3H, 2xt), 3.35-3.48 (2H, m), 3.69-3.91 and 4.28-4.32 (2H, 2xm), 3.80 and 3.87 (3H, 2xs), 5.13 and 5.47 (1H, dd *J* 4.0 and 6.6 Hz and approx. t, *J* 6.4 Hz), 6.33 and 6.41 (1H, 2xs), 7.28-7.37 (3H, m, Ar-H), 7.51-7.53 and 7.63-7.66 (2H, m, Ar-H); m/z 323 (M^+, 4%), 237 (51), 222 (100), 162 (41), 121 (48), 104 (41), 86 (26), 77 (21) and 59 (23). $[\alpha]_D^{25}$ = + 189 (c = 0.1, CH_2Cl_2).

Anal. Calcd. for $C_{15}H_{17}NO_5S$: C, 55.7; H, 5.3; N, 4.3; S, 9.9. Found: C, 56.1; H, 5.6; N, 4.5; S, 9.8.

N (1-Ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine (**4**).

A solution of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid **3a** (5 mmol) in Ac_2O (20 mL) was 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)]. A mixture of (2*S*)-*N*-(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine and (2*R*)-*N*-(1-ethoxycarbonyl-2-phenylvinyl)-2-phenyl-4-thioxo-1,3-thiazolidine was isolated in 18% yield, mp 117-119 ºC (from ethyl ether-hexane). ^{1}H nmr (two rotamers are detected): δ 1.18 and 1.38 (3H, 2xt), 4.02-4.60 (4H, m), 5.72 and 6.22 (1H, 2xs), 6.89-7.48 (10H, m, Ar-H), 7.63 (1H, s); m/z 369 (M^+, 21%), 247 (49), 201 (35), 174 (100), 121 (25), 77 (15). $[\alpha]_D^{25}$ = - 152 (c = 0.1, CH_2Cl_2).

Anal. Calcd. For $C_{20}H_{19}NO_2S_2$: C, 65.0; H, 5.2; N, 3.8. Found: C, 65.0; H, 5.3; N, 3.7.

Ethyl Cinnamate (**13**).

A solution of (2*R*,4*R*)-*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid **3a** (5 mmol) in Ac_2O (20 mL) was heated in a sealed tube at 200 °C for 2 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 preparative tlc [hexane-ethyl acetate (5:1)]. Ethyl cinnamate was isolated as an oil in 32% yield. ^{1}H nmr: δ 1.34 (3H, t), 4.27 (2H, q), 6.44 (1H, d, *J* 16 Hz), 7.36-7.40 (2H, m, Ar-H), 7.48-7.55 (3H, m, Ar-H), 7.69 (1H, d, *J* 16 Hz); m/z 176 (M^+, 30%), 148 (15), 131 (100), 103 (46) and 77 (28).

5-Ethyl 6,7-Dimethyl (*3R*)-3-Phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-5,6,7-tricarboxylate (**14**).

(2*R*,4*R*) -*N*-ethoxyoxalyl-2-phenylthiazolidine-4-carboxylic acid **3a** (5 mmol), dimethyl acetylenedicarboxylate (7.5 mmol) and Ac_2O (20 mL) were heated at 85 ºC for 2 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 the solvent 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)] giving 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **14** in 1% yield. ^{1}H nmr: δ 1.16 (3H, t, *J* 7.1 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.02 (1H, q, *J* 7.1 Hz), 4.15 (1H, q, *J* 7.1 Hz), 4.35 (1H, d, *J* 16.0 Hz), 4.48 (1H, d, *J* 16.0 Hz), 6.91-6.94 (3H, m), 7.27-7.31 (3H, m); *m/z* 389 (M^+, 18%), 311 (18), 222 (11), 121 (100).

Crystal Data for Methyl (2*R*,4*R*)-*N*-Ethoxyoxalyl-2-phenylthiazolidine-4-carboxylate **3b**.

$C_{15}H_{17}NO_5S$. *M* = 323.36, monoclinic, space group $P2_1$ (# 4), *a* = 8.0421(10), *b* = 10.8572(11), *c* = 9.3248(11) Å, β = 105.40(10)° *V* = 784.96(16) Å^3, *Z* = 2, D_c = 1.368 g cm^{-3}, F_{000} = 340, μ = 0.229 mm^{-1}, *T* = 293 K. Number of independent intensities 4568 (including 2169 Friedel pairs) from colourless, transparent prism, 0.22 x 0.24 x □□ mm^3. Empirical absorption correction applied based on 9 ψ-scans, T_{min} = 0.962, T_{max} = 0.983, T_{ave} = 0.971. No significant crystal decay was detected. Structure solution by direct methods using SHELXS97 [9]. *R* = 0.0249 for 4190 reflections with *I*>2σ, R_w = 0.0664 for 4568 reflections used in the refinement and 268 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 CAD-4 diffractometer [10] using Mo Kα radiation (λ = 0.71073 Å) and □-2θ scans up to 30.01°.

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