SYNTHESIS OF METHYL 2-ACETYLAMINO-5-(1,3-DITHIAN-2-YL)THIAZOLE-4-CARBOXYLATE

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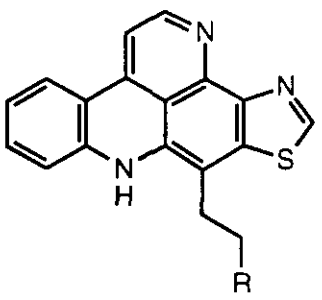
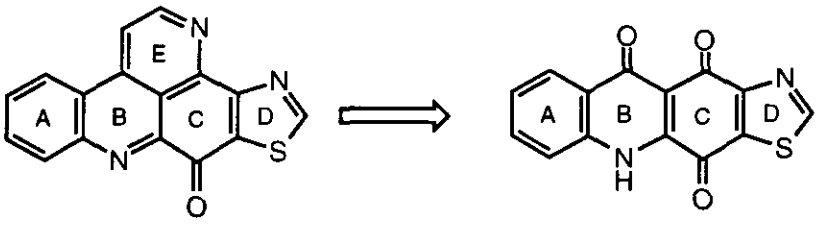
Abstract- The synthesis of methyl 2-acetylamino-5-(1,3-dithian-2-yl)thiazole-4-carboxylate (**4**) by formylation of a 4-substituted thiazole and then reaction with 1,3-propanedithiol are described. The utility of different *ortho*-directing groups (ODGs) for the lithiation of the thiazole 4-position has been studied.

Kuanoniamines[1] and dercitines[2] are highly cytotoxic thiazolopyridoacridine alkaloids obtained from marine sources.[3] Our strategy for the construction of the pentacyclic skeleton of such compounds is based on the formation of the E ring as the last step from a tetracyclic A-D ring system (**1**).[4]



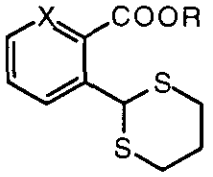
Kuanoniamine B R = NHCO*i*Pr
Kuanoniamine C R = NHCOEt
Kuanoniamine D R = NHCOMe
Nordercitine R = NMe_2
Dercitamine R = NHMe

We have studied[4-6] several annelation processes for the preparation of linear tetracyclic A-B-C-D systems analogous to **1**. We have shown for example that methyl 2-(1,3-dithian-2-yl)benzoate (**2**) is able to react efficiently, in a bidentate sense with α,β-unsaturated ketones or α,β-unsaturated esters[5] and in particular with an *N*-protected 4-quinolone.[6]



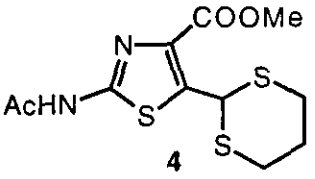
Kuanoniamine A **1**

Unfortunately the azaanalogues of **2**, methyl 3-(1,3-dithian-2-yl)pyridine-2-carboxylate (**3a**) and isopropyl 3-(1,3-dithian-2-yl)pyridine-2-carboxylate (**3b**), did not react with 4-quinolones, which was our primary objective.

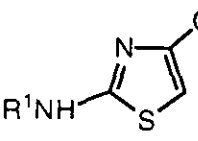


2 X = CH, R = Me
3a X = N, R = Me
3b X = N, R = *i*-Pr

However, we decided to examine the same annelation strategy for an approach to the synthesis of kuanoniamine-like marine alkaloids, hoping for a reaction between a suitable 4-quinolone and a 4,5-disubstituted thiazole such as methyl 2-acetylamino-5-(1,3-dithian-2-yl)thiazole-4-carboxylate (**4**) capable in principal of reacting in the desired bidentate sense. The function of the acetylamino group is to protect the reactive 2-position of the thiazole ring during attempts at 5-metallation.



4



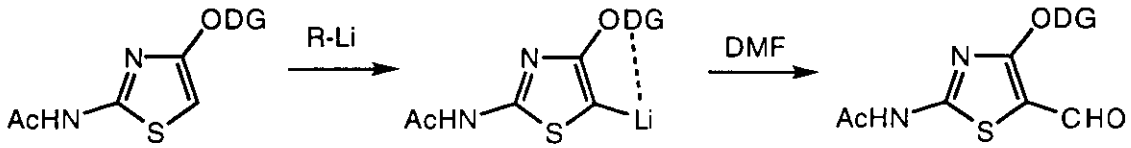
5 R^1= H, R^2= Et
6a R^1= Ac, R^2= Et
6b R^1= Ac, R^2= Me

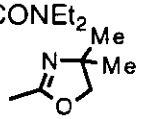
Obvious precursors for **4** – alkyl 2-acetylamino-5-formylthiazole-4-carboxylates – have not been described in the literature, nor have simpler alkyl 2-acetylaminothiazole-4-carboxylates (**6**) or their corresponding amines (**5**).

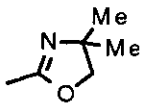
Compound (**6a**) was prepared by condensation of thiourea with ethyl bromopyruvate in ethanol, by the method described[7] for the preparation of the methyl and ethyl esters of 2-(2-amino-4-thiazolyl)acetic acid, followed by acetylation with acetic anhydride. The transformation of **6a** into **6b** was achieved by hydrolysis with aqueous lithium hydroxide, formation of the acyl chloride with thionyl chloride, and then reaction with methanol.

Classical Vilsmeier reaction is well established as a route for the synthesis of aldehydes of thiophenes[8] and pyrroles[9] but there are no precedents for its application to thiazoles and indeed our attempts at using that procedure for the formylation of **6b** yielded only unchanged starting material.

In view of this result, we decided to introduce the formyl group *via* lithiation, assisted by an *ortho*-directing group (ODG),[10] and quenching with dimethylformamide, as is well known for many aromatic and heteroaromatic compounds.[11]



	ODG
7	COOH
8	$CONHC_6H_5$
9	$CONEt_2$
10	
11	$CONHCMe_2CH_2OH$

	ODG
12a	$CONHC_6H_5$
12b	$CONEt_2$
12c	

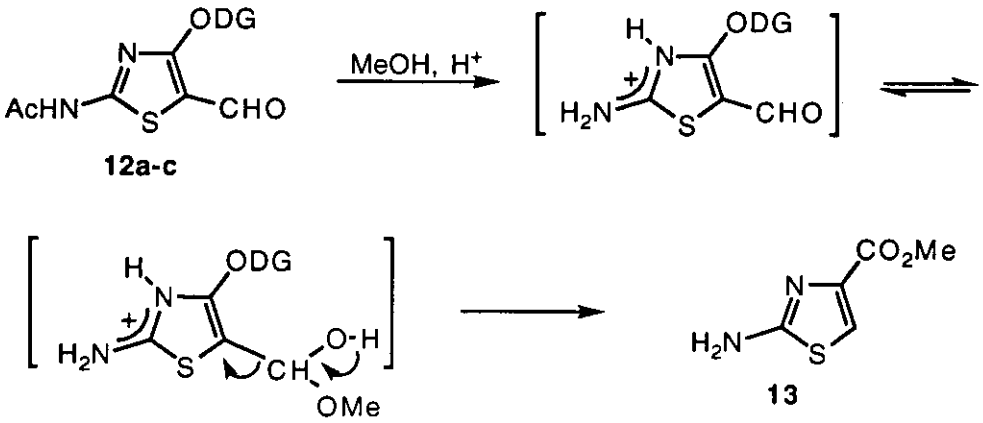
Scheme 1

We chose as ODG the carboxylic acid group and its derivatives as in **7**, its methyl ester (**6b**), *N*-phenylamide (**8**), *N,N*-diethylamide (**9**) and the dimethyloxazoline (**10**). The preparation of oxazoline (**10**) involves the synthesis of the amide (**11**). Amides (**8**, **9** and **11**) have not been described but they were readily prepared from **7**, in reasonable yields, by conversion into the acyl chloride, and then reaction with the appropriate amine.

Attempts to introduce the formyl group at the 5-position of **6b** and **7** by *ortho*-lithiation, and then quenching with dimethylformamide under different conditions were unsuccessful, however compounds (**8**, **9** and **10**) afforded their 5-formyl derivatives (**12a-c**) by reaction in tetrahydrofuran. The yield of **12a** was 64% when the reaction was performed on a small scale, however on a scale of 1.5 g the purification of **12a** was impossible. Aldehyde (**12b**) was obtained in 83% yield without any significant problem but **10** was converted into **12c** in a yield of only 13%, accompanied by significant amounts of starting material, which however could be easily recovered by column chromatography.

Unfortunately, when compounds (**12a-c**) were treated with methanol in sulfuric acid hoping to convert the ODG into the methyl ester as a prelude to the formation of the 1,3-dithiane from the aldehyde, only methyl 2-aminothiazole-4-carboxylate (**13**) was obtained in a yield as high as

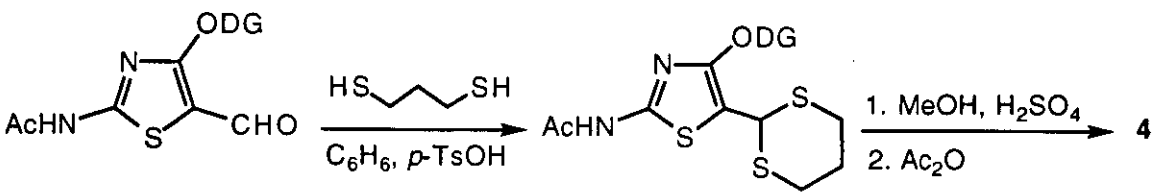
98% in some cases. The strong electron-withdrawing character of the thiazolium cation formed in the acidic medium of the reaction may provide the explanation for the deformylation reaction.

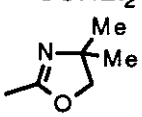


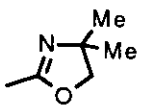
12a-c **13**

Scheme 2

Compound (**4**) was eventually prepared by reversal of the reaction order: formation of the thioketal moiety before the conversion the ODG into the methyl ester. Treatment of **12a-c** with 1,3-propanedithiol and a catalytic quantity of *p*-toluenesulfonic acid in benzene as a solvent afforded **14a-c**. When **14b** and **14c** were refluxed with sulfuric acid in methanol, only the quantitative methanolysis of the 2-acetamido group took place. However, **14a** was converted into **4** using the same conditions of methanolysis then subsequent reacetylation of the amino group.



	ODG
12a	$CONHC_6H_5$
12b	$CONEt_2$
12c	

	ODG
14a	$CONHC_6H_5$
14b	$CONEt_2$
14c	

That metallation of **4** with *n*-BuLi took place as desired at the 2-position of dithiane ring was confirmed by deuteration experiments. Unfortunately, this lithio derivative was not reactive enough to act as a bidentate reagent and allow the annelation processes with the 1-methoxycarbonyl-4-quinolone or chalcone under conditions comparable to those which were successful using **2**.[5,6]

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica Gel 60 F_{254}, Merck 0.063-0.200 mm) and spots were located with iodoplatinate reagent or UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.060-0.2 mm). Flash chromatography was carried out on SiO_2 (silica Gel 60 A CC (Merck). Organic extracts were dried over anhydrous Na_2SO_4, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were performed on a Nicolet 205 FT-IR and peaks are given in cm^{-1}. NMR spectra were measured with Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and Varian VXR-500 (500 MHz) spectrometers; data are given in δ referred to TMS with ^{1}H-NMR coupling constants (J) in Hz. Mass spectra were measured in the electron impact mode with a Hewlett-Packard model 5989A; ions are recorded as *m/z* with percentage abundances relative to the molecular ion given in parentheses. Elemental analyses were performed on a Carlo Erba Fisons EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

Ethyl 2-aminothiazole-4-carboxylate (5). A solution of thiourea (5 g, 65.8 mmol) and ethyl bromopyruvate (9 mL, 65.8 mmol) in ethanol (200 mL) was stirred and refluxed for 1 h. After this time the solvent was evaporated and saturated aqueous $NaHCO_3$ (300 mL) was added to the solid residue and the mixture was extracted with CH_2Cl_2. The organic solution dried and evaporated gave **5** (9.5 g, 84%) mp 164-165 °C (EtOAc). IR (KBr): 3440, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, J = 7.1 Hz, 3H); 4.35 (q, J = 7.1 Hz, 2H); 5.69 (br s, 2H, NH_2); 7.42 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 14.2 (q); 61.1 (t); 117.5 (d); 142.8 (s); 161.3 (s); 167.7 (s). MS (*m/z*, %): 193 (M+1, 6); 172 (M^+, 57); 100 (100). HRMS calcd for $C_6H_8N_2O_2S$ 172.0306, found 172.0305. Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.86; H, 4.67; N, 16.04; S, 18.56.

Ethyl 2-acetylaminothiazole-4-carboxylate (6a). A solution of **5** (1.5 g, 8.7 mmol) in Ac_2O (8 mL, 85 mmol) was stirred at 50 °C for 4 h. The reaction mixture was poured onto ice, basified with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic solution dried and evaporated gave **6a** (1.7 g, 92%) as a solid, mp 172-176 °C (EtOAc). IR (KBr): 3173, 1727, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J = 7.1 Hz, 3H); 2.25 (s, 3H); 4.37 (q, J = 7.1 Hz, 2H); 7.83 (s, 1H); 10.69 (br, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 14.2 (q); 23.0 (q); 61.3 (t); 122.1 (d); 140.9 (s); 159.3 (s); 161.3 (s); 169.3 (s). MS (m/z, %): 215 (M+1, 2); 214 (M^+, 15); 172 (100). HRMS calcd for $C_8H_{10}N_2O_3S$ 214.0412, found 214.0418. Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.75; H, 4.70; N, 12.80; S, 14.88.

2-Acetylaminothiazole-4-carboxylic (7). A solution of LiOH. H_2O (5.3 g, 127.6 mmol) in H_2O (70 mL) was added to a solution of **6a** (9.1 g, 42.5 mmol) in MeOH-THF (140 mL, 1:1) and the

reaction mixture was stirred at rt for 4 h. The organic solvent was evaporated and the residue acidified with 1N HCl. The resulting white solid was separated by filtration, washed with H_2O and dried to give **7** (7.8 g, 99%), mp 186-189 °C (MeOH). IR (KBr): 3443, 3183, 1695 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 2.13 (s, 3H); 7.93 (s, 1H); 12.41 (br, 1H). ^{13}C-NMR (DMSO-d_6, 75.4 MHz) δ 22.7 (q); 122.3 (d); 142.1 (s); 158.1 (s); 162.6 (s); 169.2 (s). MS (m/z, %): 187 (M+1, 2); 186 (M^+, 16); 144 (100). Anal. Calcd for $C_6H_6N_2O_3S$: C, 38.71; H, 3.25; N, 15.05; S, 17.22. Found: C, 38.66; H, 3.13; N, 14.82; S, 17.05.

General procedure for preparation of compounds (6b, 8, 9, and 11). A mixture of **7** (0.6 g, 3.2 mmol) and $SOCl_2$ (10 mL, 138 mmol) was stirred at reflux for 5 h. The excess of $SOCl_2$ was evaporated under reduced pressure and the residue was disolved in dry THF (15 mL) under nitrogen. Dry MeOH (15 mL) or the corresponding amine (6.4 mmol), was added and the reaction mixture was stirred for 1 h at rt. The solvent was evaporated and the residue basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic solution was washed with H_2O, dried, and evaporated to give the product.

Methyl 2-acetylaminothiazole-4-carboxylate (6b). Yield 77% as a solid, mp 128-131 °C (Et_2O). IR (KBr): 3280, 1730, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H); 3.15 (br s, 1H); 3.92 (s, 3H); 7.79 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 22.6 (q); 52.2 (q); 122.0 (d); 140.6 (s); 158.6 (s); 162.1 (s); 169.1 (s). MS (m/z, %): 201 (M+1, 3); 200 (M^+, 15); 158 (100). HRMS calcd for $C_7H_8N_2O_3S$ 200.0256, found 200.0254.

2-Acetylamino-4-phenylaminocarbonylthiazole (8). Yield 69%, as a brown solid, mp 168-169 °C (EtOAc). IR (KBr): 3200, 3100, 1677, 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ 2.25 (s, 3H); 7.13 (t, J = 7.4 Hz, 1H); 7.34 (dd, J = 7.4 and 8.4 Hz, 2H); 7.63 (d, J = 8.4 Hz, 2H); 7.83 (s, 1H); 9.31 (br, 1H). ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75.4 MHz) δ 22.4 (q); 118.5 (d); 119.9 (d); 124.4 (d); 128.8 (d); 137.3 (s); 143.9 (s); 157.8 (s); 159.6 (s); 169.0 (s). MS (m/z, %): 262 (M+1, 12); 261 (M^+, 75); 219 (100). HRMS calcd for $C_{12}H_{11}N_3O_2S$ 261.0572, found 261.0574.

2-Acetylamino-4-diethylaminocarbonylthiazole (9). The residue was purified by column chromatography. Elution with CH_2Cl_2-MeOH (99:1) gave **9** (1.1 g, 56%) as a solid, mp 163-164 °C (EtOAc). IR (KBr): 3165, 1610, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20 and 1.75 (2s, 6H); 2.26 (s, 3H); 3.51 (q, J = 7.1 Hz, 4H); 7.35 (s, 1H); 9.97 (br, 1H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 12.7 and 14.3 (2q); 22.9 (q); 40.4 and 43.1 (2t); 115.8 (d); 144.8 (s); 157.7 (s); 164.5 (s); 168.8 (s). MS (m/z, %): 242 (M+1, 6); 241 (M^+, 16); 72 (100). HRMS calcd for $C_{10}H_{15}N_3O_2S$ 241.0885, found 241.0879.

2-Acetylamino-4-(2-hydroxy-1,1-dimethylethylaminocarbonyl)thiazole (11). Yield 58% as an oil. IR (KBr): 3400, 1650, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 6H); 2.30 (s, 3H); 3.70 (s, 2H); 7.71 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 22.7 (q); 24.1 (q); 55.6 (t); 69.7 (s); 117.7 (d); 144.0 (s); 157.6 (s); 161.8 (s); 168.8 (s). MS (m/z, %): 259 (M+1, 6); 258 (M^+,100).

2-Acetylamino-4-(4,4-dimethyl-2-oxazolinyl)thiazole (10). *To a solution of* **11** *(200 mg, 0.8* mmol) in dry benzene (10 mL) $SOCl_2$ (0.08 mL, 1.2 mmol) was added and the mixture was refluxed for 2 h. The solution was cooled to rt and a suspension of KOH (98 mg, 1.7 mmol) in dry benzene was added. The resulting mixture was stirred at rt for 2 h and a saturated aqueous $NaHCO_3$ solution was added until the mixture was basic. The organic extract was dried and evaporated to afford **10** (180 mg, 94%) as a solid, mp 185-187 °C (Et_2O-Ac_2O). IR (KBr): 3400, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.51 (s, 6H); 2.32 (s, 3H); 3.89 (s, 2H); 7.74 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 23.1 (q); 25.1 (q); 51.2 (t); 54.2 (s); 117.8 (d); 143.9 (s); 157.3 (s); 160.5 (s); 168.1 (s). MS (m/z, %): 240 (M+1, 17); 239 (M^+, 18); 197 (93); 169 (100). HRMS calcd for $C_{10}H_{13}N_3O_2S$ 239.0728, found 239.0719.

General procedure for preparation of aldehydes (12a-c). *n*-BuLi (1.6 M in hexane, 1.9 mL, 3.1 mmol) was added drop by drop to a solution of the thiazole (1 mmol) in dry THF (5 mL) cooled at -78 °C under nitrogen. The resulting mixture was stirred at that temperature for 20 min. After this time dry DMF (0.15 g, 2 mmol) was added and the cooling bath was removed. H_2O (5 mL) was added then 6 N HCl until the pH was 1. The aqueous solution was extracted with CH_2Cl_2. The organic layer was dried and evaporated to give* **12**.

2-Acetylamino-4-phenylaminocarbonylthiazole-5-carboxaldehyde (12a). From **8** (200 mg, 7.7 mmol) following the general procedure **12a** (143 mg, 64%) was obtained; mp 89-90 °C (EtOAc). IR (KBr): 3357, 3165, 1680, 1665, 1637 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ 2.29 (s, 3H); 7.19 (t, *J* = 7.4 Hz, 1H); 7.40 (dd, *J* = 7.4 and 7.6 Hz, 2H); 7.67 (d, *J* = 7.6 Hz, 2H); 10.87 (s, 1H). ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75.4 MHz) δ 22.3 (q); 120.2 (d); 124.9 (d); 128.9 (d); 134.7 (s); 136.8 (s); 148.0 (s); 158.7 (s); 161.3 (s); 169.6 (s); 186.3 (d). MS (m/z, %): 290 (M+1, 12); 289 (M^+, 50); 219 (100). HRMS calcd for $C_{13}H_{11}N_3O_3S$ 289.0521, found 289.0520.

2-Acetylamino-4-diethylaminocarbonylthiazole-5-carboxaldehyde (12b). From **9** (3 g, 12.4 mmol) following the general procedure **12b** (2.8 g, 83%) was obtained as an oil. IR (Film): 3460, 1650, 1627, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.10-1.29 (m, 6H); 2.30 (s, 3H); 3.27 (q, *J* = 7.14 Hz, 2H); 3.58 (q, *J* = 7.14 Hz, 2H); 9.99 (s, 1H); 10.99 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 12.8 and 14.1 (2q); 23.0 (q); 40.2 and 43.3 (2t); 115.9 (s); 153.9 (s); 162.0 (s); 163.6 (s); 169.1 (s); 182.6 (s). MS (m/z, %): 270 (M+1, 2); 269 (M^+, 4); 72 (100). HRMS calcd for $C_{11}H_{15}N_3O_3S$ 269.0834, found 269.0835.

2-Acetylamino-4-(4,4-dimethyl-2-oxazolinyl)thiazole-5-carboxaldehyde (12c). From **10** (1 g, 4.2 mmol) following the general procedure an oil was obtained which was purified by column chromatopraphy. Elution with CH_2Cl_2 afforded **12c** (0.1 g, 13%) as a solid, mp 170-173 °C (Et_2O-Ac_2O). *IR (KBr): 3400, 1660, 1640 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.42 (s, 6H); 2.29* (s, 3H); 4.20 (s, 2H); 10.58 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 23.3 (q); 28.2 (q); 68.1 (s); 79.6 (t); 135.0 (s); 143.3 (s); 156.7 (s); 161.8 (s); 168.4 (s); 185.4 (d). MS (m/z, %): 267 (M^+, 2);

155 (100). HRMS calcd for $C_{11}H_{13}N_3O_3S$ 267.0678, found 267.0680. Anal. Calcd for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72; S, 11.99. Found: C, 49.26; H, 4.93; N, 15.58; S, 11.89.

Methyl 2-aminothiazole-4-carboxylate (13). To a solution of **12a** (2.1 g, 7.4 mmol) (or **12b** or **12c**) in dry MeOH (84 mL) conc. H_2SO_4 (7.9 mL) was added and the mixture was stirred at reflux temperature for 96 h. After this time the organic solvent was evaporated, the residue was basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic solution was dried and evaporated to afford **13** (621 mg, 53% from **12a**, 98% from **12b** and 83% from **12c**) as a solid, mp 105-106 °C (Et_2O). IR (KBr): 3405, 3300, 1703 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H); 7.40 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 52.04 (q); 117.5 (d); 142.3 (s); 161.9 (s); 168.2 (s). MS (m/z, %): 159 (M+1, 8); 158 (M^+, 84); 127 (94); 100 (100). HRMS calcd for $C_5H_6N_2O_2S$ 158.0144, found 58.0150.

General procedure for preparation of dithianes (14a-c). A solution of the aldehyde (**12**) (1 mmol), 1,3-propanedithiol (0.3 g, 3 mmol) and a catalytic amount of *p*-TsOH in dry benzene (25 mL) was stirred at reflux for 24 h. The organic solution was washed consecutively with saturated aqueous solution of $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography.

2-Acetylamino-5-(1,3-dithian-2-yl)-4-phenylaminocarbonylthiazole (14a). From **8** (2.8 g, 10.7 mmol) following the previously described general formylation procedure, a mixture (3.2 g) of amide (**8**) and aldehyde (**12a**), which could not be separated by column chromatography, was obtained. This mixture (3.2 g) was subjected to the general procedure for thioketalisation affording a mixture which was purified by column chromatography. Elution with CH_2Cl_2-MeOH (99:1) gave **14a** (1.8 g, 54%) as a solid, mp 137-140 °C (EtOAc). IR (KBr): 3350, 3200, 1671, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.95-2.25 (m, 2H); 2.24 (s, 3H); 2.89-3.20 (m, 4H); 6.86 (s, 1H); 7.13 (t, J = 8.8 Hz, 1H); 7.35 (dd, J = 8.8 and 7.4 Hz, 2H); 7.62 (d, J = 7.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 22.3 (q); 24.5 (t); 31.7 (t); 41.3 (d); 119.8 (d); 124.3 (d); 128.8 (d); 136.8 (s); 137.2 (s); 155.5 (s); 159.8 (s); 159.9 (s); 169.0 (s). MS (m/z, %): 380 (M+1, 4); 379 (M^+, 16); 286 (100). HRMS calcd for $C_{16}H_{17}N_3O_2S_3$ 379.0483, found 379.0489. Elution with CH_2Cl_2-MeOH (98:2) gave the amide (**8**) (0.5 g, 18%).

2-Acetylamino-4-diethylaminocarbonyl-5-(1,3-dithian-2-yl)thiazole (14b). From **12b** (343 mg, 1.3 mmol) following the general procedure, elution with CH_2Cl_2-MeOH (98:2) afforded **14b** (225 mg, 48%) as a solid, mp 109-110 °C (EtOAc). IR (KBr): 3164, 1605, 1537 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, J = 6.9 Hz, 3H); 1.24 (t, J = 6.9 Hz, 3H); 1.85-2.20 (m, 2H); 2.21 (s, 3H); 2.85-3.05 (m, 4H); 3.28 (q, J = 6.9 Hz, 2H); 3.54 (q, J = 6.9 Hz, 2H); 5.69 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 12.7 and 14.1 (2q); 22.9 (q); 24.4 (t); 31.4 (t); 39.8 and 43.1 (2t); 41.0 (d); 131.1 (s); 140.6 (s); 157.0 (s); 164.5 (s); 168.6 (s). MS (m/z, %): 359 (M^+, 20); 286 (100). HRMS calcd for $C_{14}H_{21}N_3O_2S_3$ 359.0796, found 359.0805.

2-Acetylamino-4-(4,4-dimethyl-2-oxazolinyl)-5-(1,3-dithian-2-yl)thiazole (14c). From **12c** (330 mg, 1.2 mmol) following the general procedure, elution with CH_2Cl_2-MeOH (98:2) afforded **14c** (100 mg, 23%) as an oil. IR (Film): 3420, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 6H); 1.90-2.21 (m, 2H); 2.28 (s, 3H); 2.88-3.17 (m, 4H); 3.69 (s, 2H); 6.77 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 23.1 (q); 24.6 (q); 24.7 (t); 31.9 (t); 41.2 (d); 56.1 (s); 70.2 (t); 136.8 (s); 137.0 (s); 154.9 (s); 162.3 (s); 167.9 (s). MS (m/z, %): 357 (M^+, 11); 286 (93); 216 (100). HRMS calcd for $C_{14}H_{19}N_3O_2S_3$ 357.0639, found 357.0642.

Methyl 2-acetylamino-5-(1,3-dithian-2-yl)thiazole-4-carboxylate (4). A solution of **14a** (1.5 g, 3.9 mmol) in dry MeOH (45 mL) and H_2SO_4 (2.7 mL) was refluxed for 72 h. After this time saturated aqueous $NaHCO_3$ was added until the mixture was basic then the solution was extracted with CH_2Cl_2. The organic solution was dried and evaporated to give a residue which was purified by flash column chromatography with CH_2Cl_2-MeOH (90:10) as eluent. Methyl 2-amino-5-(1,3-dithian-2-yl)thiazole-4-carboxylate (400 mg, 44% based on consumed starting material) as a reddish solid and **14a** (0.3 g) were obtained. A solution of the amine (400 mg, 1.4 mmol) in Ac_2O (1.5 mL) was stirred at 50 °C for 5 h. The reaction mixture was poured onto ice, basified with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give an oil which was purified by column chromatography. Elution with CH_2Cl_2-MeOH (99:1) afforded **4** (438 mg, 98%) as a red solid, mp 162-165 °C (EtOAc). IR (KBr): 3400, 2950, 1720, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.95-2.10 (m, 2H); 2.22 (s, 3H); 2.81-3.19 (m, 4H); 3.92 (s, 3H); 6.49 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 22.9 (q); 24.3 (t); 31.5 (t); 41.2 (d); 52.2 (q); 134.1 (s); 140.9 (s); 157.0 (s); 161.9 (s); 168.9 (s). MS (m/z, %): 319 (M+1, 3); 318 (M^+, 16); 286 (100). HRMS calcd for $C_{11}H_{14}N_2O_3S_3$ 318.0166, found 318.0169.

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REFERENCES

1. R. A. Carrol and P. J. Scheuer, *J. Org. Chem.*, 1990, **55**, 4426.
2. G. P. Gunawardana, S. Kohmoto, S. P. Gunasekara, O. J. McConnell, and F. E. Koehn, *J. Am. Chem. Soc.*, 1988, **110**, 4856; G. P. Gunawardana, S. Kohmoto, and N. S. Burres, *Tetrahedron Lett.*, 1989, **30**, 4359; G. P. Gunawardana, S. Koehn, A. Y. Lee, J. Clardy, H.-Y. He, and J. Faulkner, *J. Org. Chem.*, 1992, **57**, 1523.
3. For reviews of isolation, structure determination and synthesis of these compounds see: M. Alvarez, M. Salas, and J. A. Joule, *Heterocycles*, 1991, **32**, 759; M. Alvarez and J. A. Joule, *Heterocycles*, 1992, **34**, 2385; T. F. Molinski, *Chem. Rev.*, 1993, **93**, 1825; A. M. Echevarren, *Advances in Nitrogen Heterocycles*, 1996, **2**, 211.

4. W. Ajana, F. López-Calahorra, J. A. Joule, and M. Alvarez, *Tetrahedron*, 1997, **53**, 341.
5. W. Ajana, F. López-Calahorra, M. Alvarez, and J. A. Joule, *Tetrahedron Lett.*, 1992 , **33**, 3679.
6. M. Alvarez, W. Ajana, F. Lopez-Calahorra, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1994, 917.
7. E. Campaigne and T. P. Selby, *J. Heterocycl. Chem.*, 1980, **17**, 1255.
8. A. W. Weston and R. J. Michaels, *Org. Synth.*, 1951, **31**, 108.
9. R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Synth.*, 1956, **36**, 74.
10. H. W. Gschwend and H. R. Rodríguez, *Org. React.*, 1979, **26** , 1.
11. V. Snieckus, *Chem. Rev.* , 1990, **90**, 879; G. Queguiner, F. Marsais, V. Snieckus, and J. Epsztajn, *Adv. Heterocycl. Chem*, 1991, **52**, 187; M. S. South and K. A. Van Sant, *J. Heterocycl. Chem.*, 1991, **28**, 1017; B. Iddon, *Heterocycles*, 1995, **41**, 533.

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