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Synthesis of Pyrrolo[2,1-*b*]thiazol-3-one Derivatives

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Summary. Ethyl [4-oxo-3-(2-oxo-2-arylethyl)thiazolidin-2-ylidene]acetates and [4-oxo-3-(2-oxo-2-arylethyl)thiazolidin-2-ylidene]acetonitriles were shown to react with substituted benzaldehydes at the endocyclic methylene group leading to the corresponding 5-arylmethylidene derivatives. Their treatment with $DMF \cdot POCl_3$ complex yielded 3-oxo-5-aroyl-2-arylmethylidene-2,3-dihydropyrrolo[2,1-*b*]thiazole-7-carboxylic acids ethyl esters and -7-carbonitriles. The structures of the pyrrolothiazoles were confirmed by an X-ray crystallographic study, which indicated the (*Z*)-configuration at the arylmethylidene moiety.

Keywords. Aldehydes; Cyclizations; Heterocycles; Thiazole; Vilsmeyer complex.

Introduction

The pyrrolo[2,1-*b*]thiazol-5-one (**1**, Fig. 1) can be considered as the homologue of the penicillin nucleus. This was first articulated long ago [1, 2] and stimulated extensive syntheses of compounds of type **1**. At least two general approaches to this framework were elaborated, namely the ring expansion of various penicillin derivatives [3–6] and the reaction of 4-oxo-carboxylic acids or esters with 2-aminoethanethiol derivatives including cysteine and related compounds [1, 2, 7–15]. Additionally a number of more specific methods were described [16–20]. Thus, about 250 derivatives of **1** have been prepared to date. However, contrary to all expectations satisfactory antibiotics have not been found among this set. Nevertheless, potent neuroleptic [21, 22] and antidiabetic [23] drugs have been found instead and accordingly, the interest in compounds **1** increased.

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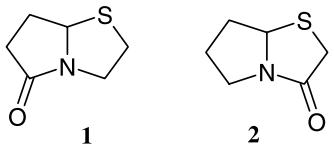
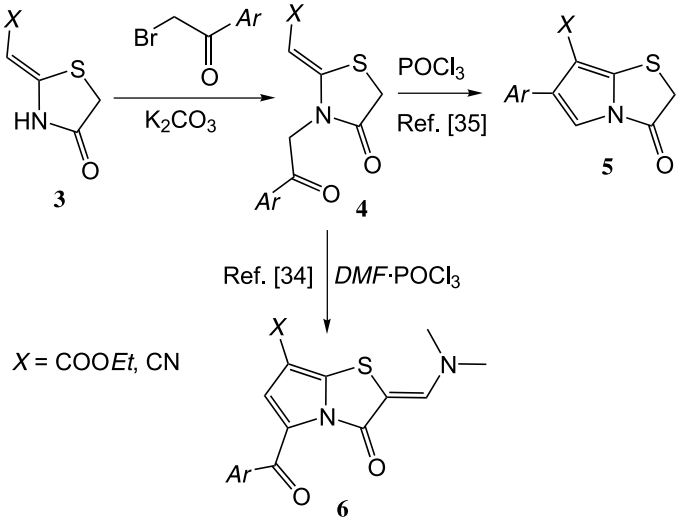


Fig. 1. The structures of isomeric pyrrolo[2,1-*b*]thiazolones

Since the presence of the endocyclic amide moiety seems to be necessary for activity [21–23] we have turned our attention to the isomeric pyrrolo[2,1-*b*]thiazol-3-one (**2**) also containing the amide bond. Unlike derivatives **1** a literature search revealed only at about 30 compounds of type **2**. Nevertheless, even within this small set compounds with antiinflammatory activity [24, 25] and a few useful for prevention and treatment of human cognitive disorders [26], such as mental retardation and *Alzheimer*'s disease, have been already found. Apparently, few published data on pyrrolo[2,1-*b*]thiazol-3-ones (**2**) are caused by a lack of convenient methods of synthesis. The two approaches to **2** are based on either reaction of 2-pyrrolidinethiones with α-halo acids derivatives [27–29] or addition of mercaptoacetic acid to 1-pyrrolines and their equivalents [24–26, 30]. However, both methods are quite limited by the number of stable and available starting materials and, therefore, do not allow to obtain series of compounds required for effective drug discovery. Other syntheses [31–33] are multi-step and very specific, and as a rule yield single substances of structure **2** with unique substitution pattern. Hence, development of new approaches to derivatives **2** providing a possibility of wide substituents variation is a promising task.

During our previous investigations we have reported [34, 35] preparation of two kinds of pyrrolo[2,1-*b*]thiazol-3-one derivatives (**5**, **6**, Scheme 1) from the readily available thiazoles **3** [36–38]. Continuing these studies, an attempt to extend the scope of the method by initial exploitation of the active methylene of



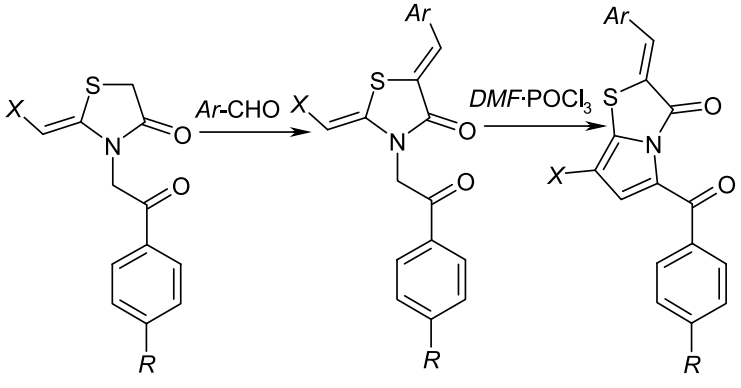
Scheme 1

the intermediates **4** and further ring closure into desired pyrrolothiazoles was examined; the results are described herein.

Results and Discussions

Compounds **7**–**10** were found to react with substituted benzaldehydes in the presence of piperidine as a catalyst at the endocyclic methylene group resulting in the corresponding arylidene derivatives **11**–**20** in 70–90% yields (Scheme 2). Similar condensations are well known for related thiazol-4(5*H*)-ones [39–44]. Noteworthy, another methylene group of **7**–**10** as well as the enamine moiety remained inactive towards the aldehydes. Following an analogy with the synthesis of pyrrolothiazoles **6** [34] **11**–**20** were treated with 2-fold excess of the $DMF \cdot POCl_3$ complex. Thus, the target pyrrolo[2,1-*b*]thiazol-3-ones **21**–**30** were obtained. Generally, the esters **11**–**16** ($X = CO_2Et$) appeared to be more reactive than the nitriles **17**–**20** ($X = CN$) and required shorter reaction times giving higher yields of **21**–**30**. Furthermore, an attempt to convert **11**–**20** into their corresponding analogues of **5** was performed but, unfortunately, it failed. Derivatives **11**–**20** were recovered unchanged after several hours refluxing in $POCl_3$. The different behavior of thiazolones **4** and their arylidene derivatives **11**–**20** in this case is believed to be connected with the possibility of the endocyclic oxomethylene moiety of **4** to enolize, which is absent for **11**–**20**. The enolization allows to avoid the amide structure, thus increasing the reactivity of the enamine fragment and facilitating its intramolecular interaction with the carbonyl. At the same time the reactivity of the enamides **11**–**20** turned out to be high enough for the formylation reaction and formation of **21**–**30**.

The structures of **11**–**20** and **21**–**30** were confirmed by ^1H and ^{13}C NMR data. For selected samples 2D NMR experiments (HSQC, HMBC) were performed to



7-10 **11-20** **21-30**

$X = CO_2Et$ **7,8,11-16,21-26** CN **9,10,17-20,27-30**

R = H **7,9,11-13,17,18,21-23,27,28** Cl **8,10,14-16,19,20,24-26,29,30**

Ar = 4-$MeOC_6H_4$ **11,14,17,19,21,24,27,29**
4-$(Me_2N)C_6H_4$ **12,15,18,20,22,25,28,30**
4-ClC_6H_4 **13,16,23,26**

Scheme 2

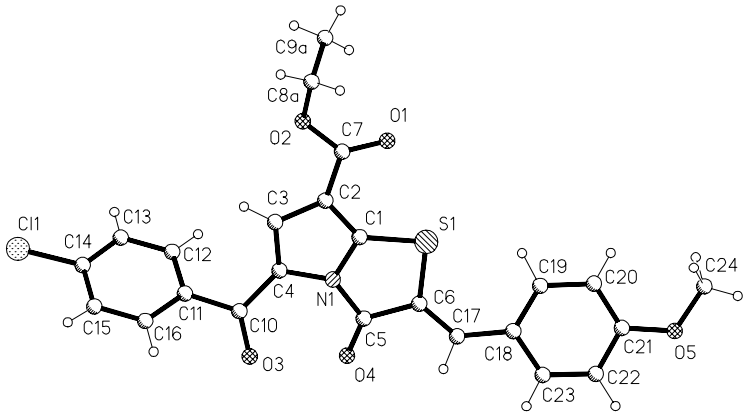


Fig. 2. X-Ray molecular structure of **24** with the atom numbering used in the crystallographic analysis

facilitate signals assignment. However, it should be noted that condensation of thiazolones **7**–**10** with aldehydes afforded derivatives **11**–**20** as single stereoisomers of either (*E*)- or (*Z*)-configuration. Moreover, after the cyclization step the configuration remained, thus, **21**–**30** were also obtained as single stereoisomers. Since the spectral data did not allow a stereochemical assignment an X-ray crystallographic study was carried out for **24** (Fig. 2). It indicated the (*Z*)-configuration. Accordingly, the same stereochemistry has to be assigned throughout the series of **21**–**30** and their precursors **11**–**20**. Exclusive formation of (*Z*)-isomers **11**–**20** during condensation with aldehydes seems to be driven by thermodynamic factors.

According to the crystal data the pyrrolothiazole system is almost planar (deviations from the least-square do not exceed 0.05 Å). Bond distances and angles are typical for conjugated heterocycles. The sum of the bond angles around N1 is 359.7(2)° thus demonstrating the conjugation of its lone pair with the heterocyclic core.

In conclusion, the present investigation has resulted in a convenient method for the preparation of pyrrolo[2,1-*b*]thiazol-3-ones **21**–**30** with at least three points of substituents variation. In fact, the targets **21**–**30** were obtained in three steps from the readily available thiazoles **3** [36–38]. The other reagents used are also of general access and the procedure is simple. The overall yields of **21**–**30** from thiazoles **3** achieved 45–50%. So, the elaborated approach provides an opportunity of easy synthesis of an ensemble of pyrrolo[2,1-*b*]thiazol-3-ones that is suitable for a drug discovery process.

Experimental

Compounds **7**–**10** were prepared as reported [34]. The aldehydes were commercially available. *DMF* was kept over P_2O_5 overnight and distilled under reduced pressure. All melting points were determined in open capillary tubes in a *Thiele* apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in *DMSO*-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si; *J* values are in Hz. 2D NMR experiments were performed on a Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument. For all compounds satisfactory elemental analyses were obtained.

5-Arylmethylidene-4-oxo-3-phenacylthiazoles (**11**–**20**). *General Procedure*
Piperidine (0.1 cm^3) was added to a solution of 5 mmol **7**–**10** and 5 mmol of the appropriate aldehyde in 3 cm^3 DMF. The mixture was heated at 120–130°C for 1.5–3.0 h. After cooling, the precipitate formed was filtered off and dried at 100°C/15 mm Hg to give **11**–**20**, which were of sufficient purity for use on further step. Analytical samples were recrystallized from *DMF* or aqueous *DMF*.

Ethyl [5-(4-methoxyphenyl)methylidene-4-oxo-3-(2-oxo-2-phenylethyl)thiazolidin-2-ylidene]acetate (**11**, $C_{23}H_{21}NO_5S$)
Yield 82% (1.74 g), mp 224–225°C; ^{1}H NMR: $\delta = 1.19$ (t, $J = 6.8$ Hz, CH_3), 3.84 (s, OCH_3), 4.11 (q, $J = 6.8$ Hz, OCH_2), 5.57 (s, NCH_2), 5.93 (s, 2-CH), 7.15 (d, $J = 9.2$ Hz, Ar), 7.60 (t, $J = 7.6$ Hz, COPh), 7.66 (m, 5-CH, Ar), 7.74 (t, $J = 7.6$ Hz, COPh), 8.08 (d, $J = 7.6$ Hz, COPh) ppm; ^{13}C NMR: $\delta = 16.1$ (CH_3), 53.4 (NCH_2), 55.1 (OCH_3), 57.3 (OCH_2), 88.5 (CHCOO), 115.2 (3,5-C_{Ar}), 122.8 (C = CHAr), 126.3 (2,6-C_{COPh}), 127.0 (1-C_{Ar}), 128.0 (3,5-C_{COPh}), 132.3 (2,6-C_{Ar}), 133.0 (4-C_{COPh}), 134.7 (1-C_{COPh}), 137.6 (CHAr), 152.5 (C = CHCOO), 160.5 (4-C_{Ar}), 165.4 (COO), 165.7 (CON), 191.0 (COAr) ppm.

Ethyl {5-[4-(dimethylamino)phenyl]methylidene-4-oxo-3-(2-oxo-2-phenylethyl)thiazolidin-2-ylidene}acetate (**12**, $C_{24}H_{24}N_2O_4S$)
Yield 87% (1.90 g), mp 284–285°C; ^{1}H NMR: $\delta = 1.19$ (t, $J = 7.2$ Hz, CH_3), 3.03 (s, NMe_2), 4.11 (q, $J = 7.2$ Hz, OCH_2), 5.55 (s, NCH_2), 5.84 (s, 2-CH), 6.87 (d, $J = 8.4$ Hz, Ar), 7.53 (d, $J = 8.4$ Hz, Ar), 7.58 (s, 5-CH), 7.61 (t, $J = 7.2$ Hz, COPh), 7.74 (t, $J = 7.2$ Hz, COPh), 8.10 (d, $J = 7.2$ Hz, COPh) ppm; ^{13}C NMR: $\delta = 14.4$ (CH_3), 39.9 (NMe_2), 51.0 (NCH_2), 57.6 (OCH_2), 91.4 (CHCOO), 112.4 (1-C_{Ar}), 113.0 (3,5-C_{Ar}), 122.6 (C = CHAr), 127.1 (2,6-C_{COPh}), 128.0 (3,5-C_{COPh}), 129.9 (2,6-C_{Ar}), 132.9 (4-C_{COPh}), 135.4 (1-C_{COPh}), 137.5 (CHAr), 151.6 (C = CHCOO), 152.0 (4-C_{Ar}), 166.4 (CON), 167.3 (COO), 191.0 (COPh) ppm.

Ethyl [5-(4-chlorophenyl)methylidene-4-oxo-3-(2-oxo-2-phenylethyl)thiazolidin-2-ylidene]acetate (**13**, $C_{22}H_{18}ClNO_4S$)
Yield 85% (1.82 g), mp 238–239°C; ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.6$ Hz, CH_3), 4.12 (q, $J = 7.6$ Hz, OCH_2), 5.60 (s, NCH_2), 6.01 (s, 2-CH), 7.61 (t, $J = 8.0$ Hz, COPh), 7.65 (d, $J = 8.4$ Hz, Ar), 7.70 (s, 5-CH), 7.71–7.77 (m, Ar, COPh), 8.09 (d, $J = 8.0$ Hz, COPh) ppm; ^{13}C NMR: $\delta = 15.0$ (CH_3), 50.3 (NCH_2), 57.2 (OCH_2), 90.0 (CHCOO), 119.5 (C = CHAr), 128.0 (2,6-C_{COPh}), 128.7 (3,5-C_{COPh}), 129.0 (3,5-C_{Ar}), 131.0 (1-C_{Ar}), 131.7 (4-C_{Ar}), 132.5 (4-C_{COPh}), 134.4 (2,6-C_{Ar}), 135.4 (1-C_{COPh}), 138.4 (CHAr), 151.5 (C = CHCOO), 166.0 (CON), 166.2 (COO), 188.8 (COPh) ppm.

Ethyl {3-[2-(4-chlorophenyl)-2-oxoethyl]-5-(4-methoxyphenyl)methylidene-4-oxothiazolidin-2-ylidene}acetate (**14**, $C_{23}H_{20}ClNO_5S$)
Yield 90% (2.06 g), mp 214–215°C; ^{1}H NMR: $\delta = 1.19$ (t, $J = 7.2$ Hz, CH_3), 3.84 (s, OCH_3), 4.12 (q, $J = 7.2$ Hz, OCH_2), 5.55 (s, NCH_2), 5.93 (s, 2-CH), 7.15 (d, $J = 9.0$ Hz, Ar), 7.64–7.69 (m, Ar, COAr, 5-CH), 8.10 (d, $J = 8.7$ Hz, COAr) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 50.1 (NCH_2), 55.0 (OCH_3), 59.7 (OCH_2), 90.9 (CHCOO), 115.1 (3,5-C_{Ar}), 120.5 (C = CHAr), 127.0 (1-C_{Ar}), 128.9 (3,5-C_{COAr}), 129.9 (2,6-C_{COAr}), 130.3 (2,6-C_{Ar}), 132.7 (1-C_{COAr}), 139.1 (4-C_{COAr}) 140.2 (CHAr), 151.6 (C = CHCOO), 158.7 (4-C_{Ar}), 165.8 (CON), 166.7 (COO), 190.5 (COAr) ppm.

Ethyl {3-[2-(4-chlorophenyl)-2-oxoethyl]-5-[4-(dimethylamino)phenyl]methylidene-4-oxothiazolidin-2-ylidene}acetate (**15**, $C_{24}H_{23}ClN_2O_4S$)
Yield 82% (1.93 g), mp 283°C; ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.2$ Hz, CH_3), 3.03 (s, NMe_2), 4.12 (q, $J = 7.2$ Hz, OCH_2), 5.53 (s, NCH_2), 5.84 (s, 2-CH), 6.87 (d, $J = 8.8$ Hz, Ar), 7.53 (d, $J = 8.8$ Hz, Ar), 7.58 (s, 5-CH), 7.68 (d, $J = 8.4$ Hz, COAr), 8.10 (d, $J = 8.4$ Hz, COAr) ppm; ^{13}C NMR: $\delta = 15.0$ (CH_3), 39.0 (NMe_2), 52.0 (NCH_2), 59.0 (OCH_2), 88.6 (CHCOO), 112.7 (1-C_{Ar}), 114.7 (3,5-C_{Ar}), 119.4

(C = CHAr), 127.4 (3,5-C_{COAr}), 128.5 (2,6-C_{COAr}), 133.7 (2,6-C_{Ar}), 134.7 (1-C_{COAr}), 138.7 (CHAr), 139.0 (4-C_{COAr}) 150.3 (C = CHCOO), 151.0 (4-C_{Ar}), 162.7 (CON), 166.0 (COO), 189.2 (COAr) ppm.

Ethyl {5-(4-chlorophenyl)methylidene-3-[2-(4-chlorophenyl)-2-oxoethyl]-4-oxothiazolidin-2-ylidene}acetate (**16**, $C_{22}H_{17}Cl_2NO_4S$)
Yield 81% (1.87 g), mp 225–226°C; ^{1}H NMR: $\delta = 1.19$ (t, $J = 6.8$ Hz, CH_3), 4.12 (q, $J = 6.8$ Hz, OCH_2), 5.59 (s, NCH_2), 6.03 (s, 2-CH), 7.64–7.73 (m, Ar, COAr, 5-CH), 8.10 (d, $J = 9.2$ Hz, COAr) ppm; ^{13}C NMR: $\delta = 16.3$ (CH_3), 52.2 (NCH_2), 60.1 (OCH_2), 92.6 (CHCOO), 118.8 (C = CHAr), 127.6 (2,6-C_{COAr}), 128.0 (3,5-C_{COAr}), 131.0 (1-C_{COAr}), 131.5 (3,5-C_{Ar}), 132.6 (4-C_{Ar}), 132.9 (1-C_{Ar}), 133.0 (2,6-C_{Ar}), 136.5 (CHAr), 139.0 (4-C_{COAr}) 153.4 (C = CHCOO), 167.8 (CON), 168.7 (COO), 190.9 (COAr) ppm.

[5-(4-Methoxyphenyl)methylidene-4-oxo-3-(2-oxo-2-phenylethyl)thiazolidin-2-ylidene]acetonitrile (**17**, $C_{21}H_{16}N_2O_3S$)
Yield 85% (1.60 g), mp 209–210°C; ^{1}H NMR: $\delta = 3.86$ (s, OCH_3), 5.48 (s, NCH_2), 5.69 (s, 2-CH), 7.15 (d, $J = 9.6$ Hz, Ar), 7.62 (m, Ar, COPh), 7.74 (t, $J = 7.6$ Hz, COPh), 7.76 (s, 5-CH), 8.07 (d, $J = 7.6$ Hz, COPh) ppm; ^{13}C NMR: $\delta = 49.0$ (NCH_2), 56.0 (OCH_3), 71.3 (CHCN), 118.1 (3,5-C_{Ar}), 118.3 (CN), 119.9 (C = CHAr), 127.1 (1-C_{Ar}), 127.5 (2,6-C_{COPh}), 128.2 (3,5-C_{COPh}), 131.0 (2,6-C_{Ar}), 132.9 (1-C_{COPh}), 133.0 (4-C_{COPh}), 140.0 (CHAr), 153.9 (C = CHCN), 158.0 (4-C_{Ar}), 165.4 (CON), 188.5 (COPh) ppm.

{5-[4-(Dimethylamino)phenyl]methylidene-4-oxo-3-(2-oxo-2-phenylethyl)thiazolidin-2-ylidene}acetonitrile (**18**, $C_{22}H_{19}N_3O_2S$)
Yield 73% (1.42 g), mp 247–248°C; ^{1}H NMR: $\delta = 3.04$ (s, NMe_2), 5.47 (s, NCH_2), 5.64 (s, 2-CH), 6.88 (d, $J = 6.8$ Hz, Ar), 7.50 (d, $J = 6.8$ Hz, Ar), 7.61 (t, $J = 7.2$ Hz, COPh), 7.68 (s, 5-CH), 7.75 (t, $J = 7.2$ Hz, COPh), 8.08 (d, $J = 7.2$ Hz, COPh) ppm; ^{13}C NMR: $\delta = 39.9$ (NMe_2), 49.8 (NCH_2), 68.2 (CHCN), 111.4 (1-C_{Ar}), 112.2 (3,5-C_{Ar}), 117.4 (CN), 119.9 (C = CHAr), 128.4 (3,5-C_{COPh}), 128.9 (2,6-C_{COPh}), 132.2 (2,6-C_{Ar}), 132.4 (4-C_{COPh}), 134.3 (1-C_{COPh}), 138.5 (CHAr), 151.5 (4-C_{Ar}), 154.7 (C = CHCN), 165.8 (CON), 191.0 (COPh) ppm.

{3-[2-(4-Chlorophenyl)-2-oxoethyl]-5-(4-methoxyphenyl)methylidene-4-oxothiazolidin-2-ylidene}acetonitrile (**19**, $C_{21}H_{15}ClN_2O_3S$)
Yield 71% (1.46 g), mp 227°C; ^{1}H NMR: $\delta = 3.85$ (s, OCH_3), 5.51 (s, NCH_2), 5.78 (s, 2-CH), 7.16 (d, $J = 8.8$ Hz, Ar), 7.65 (d, $J = 8.8$ Hz, Ar), 7.70 (d, $J = 8.4$ Hz, COAr), 7.79 (s, 5-CH), 8.10 (d, $J = 8.4$ Hz, COAr) ppm; ^{13}C NMR: $\delta = 49.4$ (NCH_2), 55.8 (OCH_3), 69.2 (CHCN), 115.9 (3,5-C_{Ar}), 118.2 (CN), 119.0 (C = CHAr), 127.0 (1-C_{Ar}), 129.5 (2,6-C_{COAr}), 131.0 (2,6-C_{Ar}), 131.2 (3,5-C_{COAr}), 132.6 (1-C_{COAr}), 134.2 (4-C_{COAr}) 141.2 (CHAr), 156.3 (C = CHCN), 158.4 (4-C_{Ar}), 165.3 (CON), 194.4 (COAr) ppm.

{3-[2-(4-Chlorophenyl)-2-oxoethyl]-5-[4-(dimethylamino)phenyl]-methylidene-4-oxothiazolidin-2-ylidene}acetonitrile (**20**, $C_{22}H_{18}ClN_3O_2S$)
Yield 87% (1.84 g), mp 263°C; ^{1}H NMR: $\delta = 3.03$ (s, NMe_2), 5.46 (s, NCH_2), 5.63 (s, 2-CH), 6.86 (d, $J = 8.8$ Hz, Ar), 7.48 (d, $J = 8.8$ Hz, Ar), 7.67 (s, 5-CH), 7.69 (d, $J = 8.0$ Hz, COAr), 8.08 (d, $J = 8.0$ Hz, COAr) ppm; ^{13}C NMR: $\delta = 39.8$ (NMe_2), 49.1 (NCH_2), 67.2 (CHCN), 110.7 (1-C_{Ar}), 113.3 (3,5-C_{Ar}), 115.2 (CN), 119.0 (C = CHAr), 128.0 (3,5-C_{COAr}), 130.3 (2,6-C_{COAr}), 131.5 (2,6-C_{Ar}), 132.0 (1-C_{COAr}), 136.4 (4-C_{COAr}) 138.4 (CHAr), 151.7 (4-C_{Ar}), 155.7 (C = CHCN), 163.1 (CON), 188.9 (COAr) ppm.

3-Oxo-5-aroyl-2-arylmethylidene-2,3-dihydropyrrolo[2,1-b]thiazoles (**21**–**30**). *General Procedure*
Compound **11**–**20** (2 mmol) was added to a solution of 0.61 g $POCl_3$ (4 mmol) in 3 cm^3 *DMF* and the resulting mixture was heated at 100–110°C for 1.5–2.0 h. After cooling the solid formed was

filtered off, washed sequentially with H_2O, saturated aqueous $NaHCO_3$, and H_2O again, and air-dried. Recrystallization from *DMF* afforded **21**–**30**. An additional portion of the product could be obtained by pouring the reaction mixture filtrate into H_2O and further elaboration of the precipitated solid as above.

Ethyl 2-(4-methoxyphenyl)methylidene-3-oxo-5-phenylcarbonyl-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**21**, $C_{24}H_{19}NO_5S$)
Yield 73% (0.63 g), mp 208–209°C; ^{1}H NMR: $\delta = 1.31$ (t, $J = 6.8$ Hz, CH_3), 3.86 (s, OCH_3), 4.29 (q, $J = 6.8$ Hz, OCH_2), 7.15 (m, Ar, 6-H), 7.57 (t, $J = 7.6$ Hz, COPh), 7.70 (m, Ar, COPh), 7.88 (d, $J = 7.6$ Hz, COPh), 8.00 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 24.0$ (CH_3), 56.0 (OCH_3), 58.3 (OCH_2), 112.7 (7-C), 114.8 (3,5-C_{Ar}), 123.1 (2-C), 125.9 (6-C), 128.4 (2,6-C_{COPh}), 129.6 (1-C_{Ar}), 130.6 (3,5-C_{COPh}), 132.0 (1-C_{COPh}), 132.6 (2,6-C_{Ar}), 138.1 (5-C), 136.3 (4-C_{COPh}), 138.6 (<u>C</u>HAr), 141.5 (7a-C), 158.4 (4-C_{Ar}), 162.5 (3-CO), 163.1 (COO), 185.6 (<u>C</u>OPh) ppm.

Ethyl 2-[4-(dimethylamino)phenyl]methylidene-3-oxo-5-phenylcarbonyl-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**22**, $C_{25}H_{22}N_2O_4S$)
Yield 78% (0.70 g), mp 253–254°C; ^{1}H NMR (in CF_3COOD): $\delta = 1.53$ (t, $J = 7.0$ Hz, CH_3), 3.57 (s, NMe_2), 4.58 (q, $J = 7.0$ Hz, OCH_2), 7.62–7.70 (m, 6-H, COPh), 7.83 (t, $J = 6.6$ Hz, COPh), 7.90 (d, $J = 7.5$ Hz, Ar), 8.01 (m, Ar, COPh), 8.34 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 19.9$ (CH_3), 39.3 (NMe_2), 61.0 (OCH_2), 109.7 (7-C), 111.8 (3,5-C_{Ar}), 115.0 (2-C), 119.1 (1-C_{Ar}), 123.1 (6-C), 128.0 (3,5-C_{COPh}), 128.9 (2,6-C_{COPh}), 129.5 (2,6-C_{Ar}), 135.4 (5-C), 135.7 (1-C_{COPh}), 135.9 (4-C_{COPh}), 139.0 (<u>C</u>HAr), 138.9 (7a-C), 154.2 (4-C_{Ar}), 159.0 (3-CO), 164.7 (COO), 183.0 (<u>C</u>OPh) ppm.

Ethyl 2-(4-chlorophenyl)methylidene-3-oxo-5-phenylcarbonyl-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**23**, $C_{23}H_{16}ClNO_4S$)
Yield 59% (0.56 g), mp 224°C; ^{1}H NMR: $\delta = 1.31$ (t, $J = 7.2$ Hz, CH_3), 4.31 (q, $J = 7.2$ Hz, OCH_2), 7.17 (s, 6-H), 7.58 (t, $J = 7.6$ Hz, COPh), 7.69 (m, Ar, COPh), 7.78 (d, $J = 7.6$ Hz, COPh), 7.90 (d, $J = 8.4$ Hz, Ar), 8.08 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 24.5$ (CH_3), 60.8 (OCH_2), 110.5 (7-C), 125.0 (2-C), 125.7 (6-C), 128.7 (3,5-C_{COPh}), 129.2 (3,5-C_{Ar}), 129.6 (2,6-C_{COPh}), 130.7 (1-C_{Ar}), 131.6 (4-C_{Ar}), 132.1 (2,6-C_{Ar}), 133.2 (1-C_{COPh}), 136.0 (5-C), 136.3 (4-C_{COPh}), 137.0 (<u>C</u>HAr), 140.1 (7a-C), 159.1 (3-CO), 161.7 (COO), 182.3 (<u>C</u>OPh) ppm.

Ethyl 5-(4-chlorophenyl)carbonyl-2-(4-methoxyphenyl)methylidene-3-oxo-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**24**, $C_{24}H_{18}ClNO_5S$)
Yield 61% (0.57 g), mp 231–232°C; ^{1}H NMR: $\delta = 1.32$ (t, $J = 7.2$ Hz, CH_3), 3.86 (s, OCH_3), 4.30 (q, $J = 7.2$ Hz, OCH_2), 7.18 (d, $J = 7.3$ Hz, Ar), 7.22 (s, 6-H), 7.63 (d, $J = 7.0$ Hz, COAr), 7.73 (d, $J = 7.3$ Hz, Ar), 7.89 (d, $J = 7.0$ Hz, COAr), 8.20 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 22.5$ (CH_3), 56.6 (OCH_3), 61.0 (OCH_2), 109.7 (7-C), 114.8 (2-C), 117.0 (3,5-C_{Ar}), 125.8 (6-C), 127.9 (1-C_{Ar}), 129.7 (3,5-C_{COAr}), 131.3 (1-C_{COAr}), 132.0 (2,6-C_{Ar}), 134.5 (2,6-C_{COAr}), 137.6 (5-C), 138.0 (<u>C</u>HAr), 140.9 (4-C_{COAr}), 141.0 (7a-C), 157.4 (4-C_{Ar}), 162.3 (3-CO), 162.7 (COO), 182.8 (<u>C</u>OAr) ppm.

Ethyl 5-(4-chlorophenyl)carbonyl-2-[4-(dimethylamino)phenyl]-methylidene-3-oxo-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**25**, $C_{25}H_{21}ClN_2O_4S$)
Yield 76% (0.73 g), mp 251°C; ^{1}H NMR: $\delta = 1.32$ (t, $J = 7.2$ Hz, CH_3), 3.06 (s, NMe_2), 4.29 (q, $J = 7.2$ Hz, OCH_2), 6.84 (d, $J = 8.4$ Hz, Ar), 7.17 (s, 6-H), 7.54 (d, $J = 8.4$ Hz, Ar), 7.62 (d, $J = 8.4$ Hz, COAr), 7.87 (m, COAr, 2-CH) ppm; ^{13}C NMR: $\delta = 21.7$ (CH_3), 39.9 (NMe_2), 60.6 (OCH_2), 109.5 (7-C), 112.2 (3,5-C_{Ar}), 115.0 (2-C), 119.6 (1-C_{Ar}), 125.6 (6-C), 128.8 (2,6-C_{Ar}), 129.6 (1-C_{COAr}), 131.0 (3,5-C_{COAr}), 133.2 (2,6-C_{COAr}), 136.0 (5-C), 138.0 (4-C_{COAr}), 139.3 (<u>C</u>HAr), 140.7 (7a-C), 152.3 (4-C_{Ar}), 159.7 (3-CO), 161.9 (COO), 181.3 (<u>C</u>OAr) ppm.

Ethyl 5-(4-chlorophenyl)carbonyl-2-(4-chlorophenyl)methylidene-3-oxo-2,3-dihydropyrrolo[2,1-b]thiazole-7-carboxylate (**26**, $C_{23}H_{15}Cl_2NO_4S$)
Yield 69% (0.65 g), mp 186°C; ^{1}H NMR: $\delta = 1.31$ (t, $J = 7.0$ Hz, CH_3), 4.29 (q, $J = 7.0$ Hz, OCH_2), 7.21 (s, 6-H), 7.62–7.68 (m, Ar, COAr), 7.75 (d, $J = 8.4$ Hz, Ar), 7.89 (d, $J = 8.4$ Hz, COAr), 8.04 (s, 2-CH) ppm. ^{13}C NMR: $\delta = 26.9$ (CH_3), 61.0 (OCH_2), 110.5 (7-C), 125.1 (6-C), 126.0 (2-C), 129.3 (1-C_{COAr}), 130.0 (3,5-C_{Ar}), 131.0 (3,5-C_{COAr}), 131.1 (2,6-C_{COAr}), 132.0 (4-C_{Ar}), 132.7 (1-C_{Ar}), 134.7 (2,6-C_{Ar}), 137.8 (5-C), 138.0 (4-C_{COAr}), 139.2 (CHAr), 141.6 (7a-C), 158.5 (3-CO), 160.2 (COO), 183.9 (COAr) ppm.

2-(4-Methoxyphenyl)methylidene-3-oxo-5-phenylcarbonyl-2,3-dihydropyrrolo[2,1-b]thiazole-7-carbonitrile (**27**, $C_{22}H_{14}N_2O_3S$)
Yield 58% (0.45 g), mp 194°C; ^{1}H NMR: $\delta = 3.85$ (s, OCH_3), 7.14 (d, $J = 9.2$ Hz, Ar), 7.44 (s, 6-H), 7.56 (t, $J = 7.4$ Hz, COPh), 7.71 (m, COPh, Ar), 7.89 (d, $J = 7.4$ Hz, COPh), 8.03 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 57.1$ (OCH_3), 86.8 (7-C), 114.0 (CN), 116.7 (3,5-C_{Ar}), 119.4 (6-C), 126.8 (2-C), 128.4 (1-C_{Ar}), 129.4 (3,5-C_{COPh}), 130.7 (2,6-C_{COPh}), 133.0 (2,6-C_{Ar}), 134.0 (1-C_{COPh}), 134.9 (5-C), 135.3 (4-C_{COPh}), 138.1 (7a-C), 139.3 (CHAr), 158.5 (4-C_{Ar}), 162.0 (3-CO), 181.3 (COPh) ppm.

2-[4-(Dimethylamino)phenyl]methylidene-3-oxo-5-phenylcarbonyl-2,3-dihydropyrrolo[2,1-b]thiazole-7-carbonitrile (**28**, $C_{23}H_{17}N_3O_2S$)
Yield 58% (0.46 g), mp 231°C; ^{1}H NMR: $\delta = 3.06$ (s, NMe_2), 6.84 (d, $J = 8.4$ Hz, Ar), 7.44 (s, 6-H), 7.56 (m, Ar, COPh), 7.70 (t, $J = 7.4$ Hz, COPh), 7.88 (d, $J = 7.2$ Hz, COPh), 7.92 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 39.7$ (NMe_2), 91.3 (7-C), 113.0 (CN), 114.5 (3,5-C_{Ar}), 119.0 (6-C), 119.3 (1-C_{Ar}), 126.2 (2-C), 126.4 (3,5-C_{COPh}), 127.3 (2,6-C_{Ar}), 129.0 (2,6-C_{COPh}), 131.2 (1-C_{COPh}), 135.0 (5-C), 135.7 (4-C_{COPh}), 137.8 (7a-C), 139.0 (CHAr), 149.9 (4-C_{Ar}), 162.1 (3-CO), 182.7 (COPh) ppm.

5-(4-Chlorophenyl)carbonyl-2-(4-methoxyphenyl)methylidene-3-oxo-2,3-dihydropyrrolo[2,1-b]thiazole-7-carbonitrile (**29**, $C_{22}H_{13}ClN_2O_3S$)
Yield 51% (0.43 g), mp 244°C; ^{1}H NMR: $\delta = 3.86$ (s, OCH_3), 7.15 (d, $J = 8.8$ Hz, Ar), 7.53 (s, 6-H), 7.63 (d, $J = 8.4$ Hz, COAr), 7.72 (d, $J = 8.8$ Hz, Ar), 7.91 (d, $J = 8.4$ Hz, COAr), 8.06 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 55.7$ (OCH_3), 88.5 (7-C), 113.0 (CN), 115.3 (3,5-C_{Ar}), 119.1 (6-C), 124.9 (2-C), 127.7 (1-C_{Ar}), 128.9 (3,5-C_{COAr}), 129.7 (1-C_{COAr}), 131.2 (2,6-C_{COAr}), 133.1 (2,6-C_{Ar}), 135.5 (5-C), 135.6 (4-C_{COAr}), 138.6 (7a-C), 138.7 (CHAr), 159.0 (4-C_{Ar}), 162.3 (3-CO), 181.0 (COAr) ppm.

5-(4-Chlorophenyl)carbonyl-2-[4-(dimethylamino)phenyl]methylidene-3-oxo-2,3-dihydropyrrolo[2,1-b]thiazole-7-carbonitrile (**30**, $C_{23}H_{16}ClN_3O_2S$)
Yield 64% (0.56 g), mp 265–266°C; ^{1}H NMR: $\delta = 3.07$ (s, NMe_2), 6.86 (d, $J = 9.2$ Hz, Ar), 7.52 (s, 6-H), 7.59 (d, $J = 9.2$ Hz, Ar), 7.62 (d, $J = 8.8$ Hz, COAr), 7.90 (d, $J = 8.8$ Hz, COAr), 7.95 (s, 2-CH) ppm; ^{13}C NMR: $\delta = 40.5$ (NMe_2), 88.7 (7-C), 112.5 (3,5-C_{Ar}), 113.4 (CN), 119.0 (6-C), 119.6 (1-C_{Ar}), 124.4 (2-C), 126.1 (2,6-C_{Ar}), 128.6 (2,6-C_{COAr}), 129.0 (1-C_{COAr}), 130.8 (3,5-C_{COAr}), 135.2 (4-C_{COAr}), 136.6 (5-C), 139.0 (CHAr), 139.9 (7a-C), 151.8 (4-C_{Ar}), 165.9 (3-CO), 182.0 (COAr) ppm.

X-Ray Crystal Structure Determination of **24**
All crystallographic measurements were performed at room temperature on a CAD4 Enraf-Nonius diffractometer operating in the ω-2θ scan mode (the scanning rate ratio $\omega/2\theta = 1.2$). Intensity data were collected within the range $4.58 \leq \theta \leq 64.95°$ using Cu–K_α radiation ($\lambda = 1.54178$ Å). Crystal data: $C_{24}H_{18}ClNO_5S$, $M_r = 467.90$, monoclinic, $a = 11.381(2)$, $b = 11.688(3)$, $c = 16.540(5)$ Å, $\beta = 93.68(2)°$, $V = 2195.6(10)$ Å^3, $Z = 4$, space group $P\,2_1/n$, $\mu = 2.746$ mm^{-1}; 3940 reflections were measured, 3738 were unique, $R_{int} = 0.024$. Data were corrected for *Lorenz* and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares technique in anisotropic approximation for non-hydrogen atoms using the SHELXS97 [45] and SHELXL97 [46] program

packages. In the refinement 3738 reflections (3087 ones with $I \geq 2\sigma(I)$) were used. The carbon atoms C8 and C9 of the ethyl group were disordered over three positions A, B, and C with multiplicity 0.25, 0.5, and 0.25. Hydrogen atoms of this disordered group were placed at calculated positions as riding model with $U_{iso} = 1.2\,U$ supporting carbon atoms and corresponding multiplicity. All other hydrogen atoms were located in the difference *Fourier* maps and refined isotropically. Convergence was obtained at $R = 0.048$ and $R_w(F^2) = 0.1267$, GOF = 1.053 (357 refined parameters, 3 restrains for disordered atoms, observed/variable ratio 8.65). Full crystallographic data were deposited at Cambridge Crystallographic Data Center (CCDC) under reference number CCDC 258801.

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