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A NEW SYNTHESIS OF OF THIAZOLE DERIVATIVES *VIA* RING TRANSFORMATION OF 6-IMINO-*6H*-1,3-THIAZINE HYDROPERCHLORATES

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Abstract - 2-Arylthiazoles (**8**) with a cyanoacetate moiety in position 4 were synthesized by a new ring transformation reaction. Therefore 2-aryl-6-imino-*6H*-1,3-thiazinecarboxylic ester hydroperchlorates (**3**) were converted into 2-arylthiazoles (**8**) by reaction with acceptor substituted halomethanes (e.g. chloroacetonitrile, chloroacetic acid ester or phenacyl bromide). Using 2-(2-hydroxyphenyl)-*6H*-1,3-thiazinecarboxylic-acid ester hydroperchlorate (**3c**) as the starting compound the benzoxazine (**11a**) was obtained. Starting from 2-(4-chlorophenyl)-*6H*-1,3-thiazinecarboxylicacid ester hydroperchlorate (**3b**) the thiazolo[5,4-*c*]pyridine (**9e**) was the final product.

INTRODUCTION

Thiazoles with an acetic acid ester, acetic acid or acetonitril function at position 4 are of importance as pharmacologically active compounds.[1-5] Derivatives with an additional aryl residue in position 2 are used as antiinflammatory, analgesic or antipyretic drugs,[6,7] whereas thiazoles with a cyanoacetate group at position 4 were previously unknown. The use of substituted 6-imino-*6H*-1,3-thiazine hydroperchlorates offers the opportunity to prepare this type of thiazoles by a new synthetic pathway.
With these compounds the further investigation of structure-activity relationships of substituted thiazoles should be possible with the hope to gain compounds with new or improved pharmacological properties.

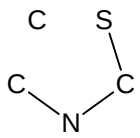
RESULTS AND DISCUSSION

Under basic conditions 6-imino-*6H*-1,3-thiazines undergo a ring opening reaction forming either acrylonitriles or acrylthioamides.[8-13] In the most cases the acrylthioamides subsequently cyclize to 4-thioxopyrimidines.[10,11,13-15]

The 6-imino-*6H*-1,3-thiazine hydroperchlorates (**3**) can be obtained by reaction of the methylthioacrylonitrile derivative (**1**) with aromatic thioamides (**2**). A special feature of **3** is the 4-methylthio group which determines the pathway of the majority of the following reactions (Scheme 3). Under basic conditions the perchloric acid is neutralised at first followed by ring opening and formation of the acrylonitriles (**6**). Starting from **6** 1,2,4-dithiazoles, 1,3-benzoxazines or 1,2,4-triazoles are preparable. In contrast thereto the ring opening to acrylthioamides (**4**) yields 1,2-dithiazoles or 4-thioxopyrimidines as final products.[16]

When 6-imino-*6H*-1,3-thiazine hydroperchlorate (**3a**) was treated with aqueous sodium hydroxide a ring opening reaction under formation of acrylthioamide (**4a**) was observed and the 4-thioxopyrimidine (**5a**) was the resulting final product.[17]

In the reaction of **3a** with aqueous sodium hydroxide/phenacyl bromide an alternative pathway is preferred: The intermediate acrylonitrile (**6**) is alkylated at the thioamide sulfur atom. Thereby the course of the ring opening reaction is driven to the formation of **6** and its reaction products. The subsequent cyclization of the intermediate thioimide acid ester (**7**) leads to the formation of the thiazole (**8d**) and methyl mercaptan. When this method is used, only small amounts of **5a** are detectable in the reaction mixture. The thiazole synthesis could be optimized by using triethylamine instead of aqueous sodium hydroxide affording the thiazole (**8d**) in a yield of more than 80 %. The use of other acceptor substituted halomethanes instead of phenacyl bromide gave the thiazoles (**8a-c**) and (**8f-i**) (see Table in Scheme 3).

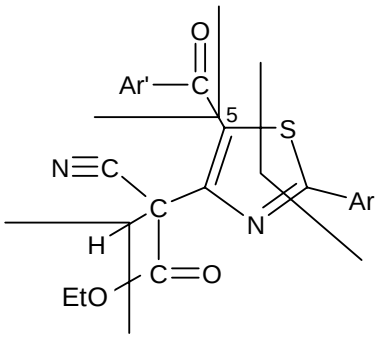


Scheme 1

The described thiazole preparation is a synthesis of the C + S-C-N-C type (Scheme 1). In comparable syntheses of this type the S-C-N-C synthon may be a part of different classes of compounds (e.g. acylthiourea derivatives, thiocarbamates or thiocarboxylates). In contrast thereto the C-synthon is always a part of an acceptor substituted halomethane as phenacyl bromide or chloroacetic acid ester. For this reason the thiazoles that were prepared by a C + S-C-N-C-synthesis always bear an acceptor group (e.g. benzoyl or carboxylic acid ester) at position 5.[18] The preparative method described in this report yields thiazoles with a carbonyl, ester or cyano

group in position 5 and a cyanoacetate group at position 4.
The methine proton of the cyanoacetate function is acid. This is indicated by the lower intensity of the ^{1}H-NMR peaks of the thiazoles at 5.91-6,37 ppm in DMSO-d_6 caused by an H-D replacement.

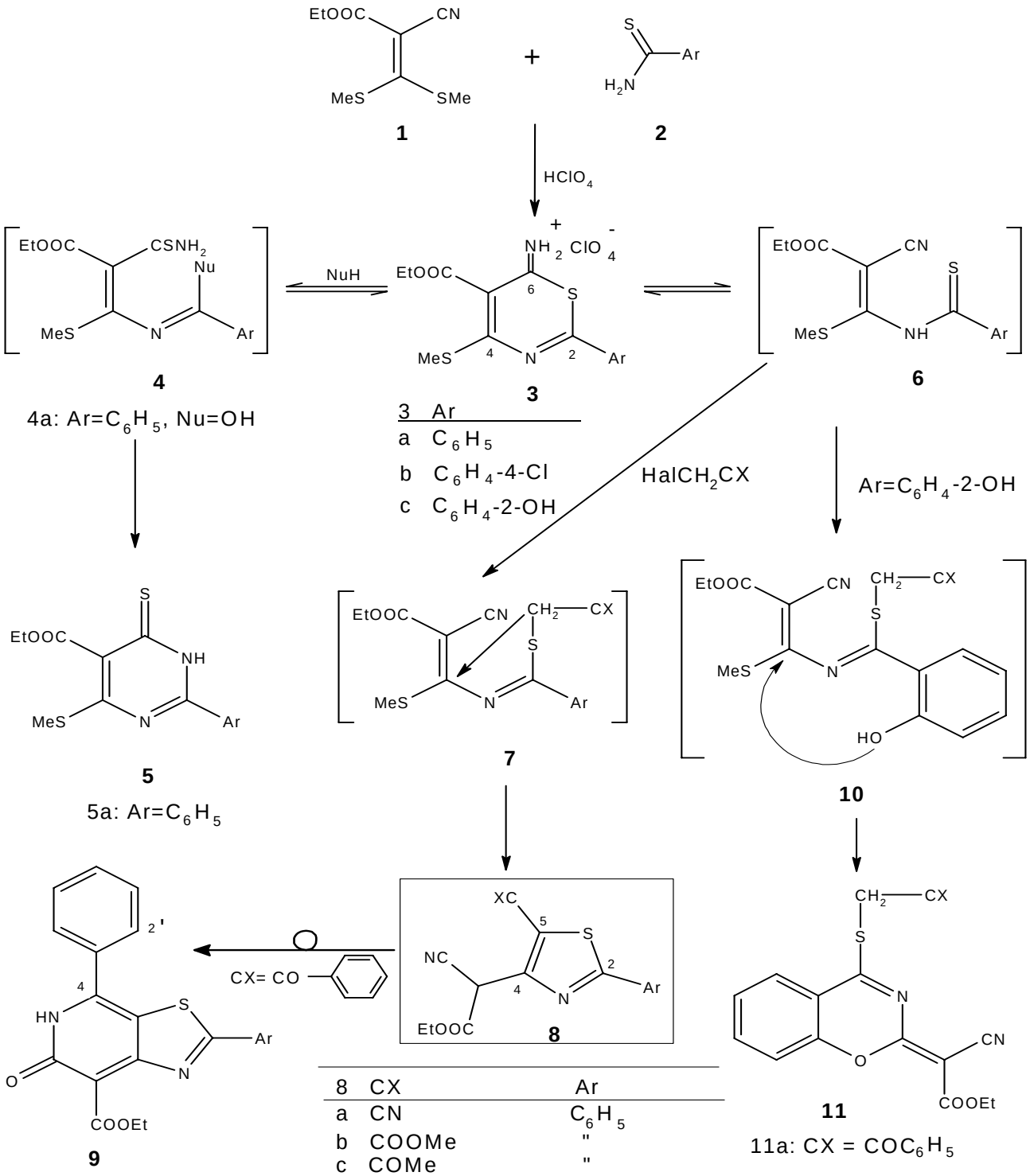
The MS spectra of the thiazoles (**8a-d**) and (**8f-i**) exhibit the molecular peaks. The spectrum of **8h** shows three peaks, the summation formula of which are in agreement with the measured results: M-46 = $[M\text{-}C_2H_5OH]^+$ (*m/z* = 375.03255), $ArCS^+$ (Ar = C_6H_5, *m/z* = 121.01345) and $Ar´CO^+$ (Ar´ = $O_2NC_6H_4$, *m/z* = 150.01562) (Scheme 2). The fragments M-46 and *m/z* = 121 are also visible in the spectra of the other synthesized thiazoles. The spectrum of compound (**8d**) is characterized by an additional metastable peak (*m/z* = 289.6*) that indicates the separation of ethanol from the molecular peak. All the thiazoles with an Ar´CO residue at position 5 are forming an $Ar'CO^+$ fragment.



Scheme 2

Depending on the aryl substituent (Ar) a distinguishing course of the preparation of some thiazoles was observed. In the case of Ar = C_6H_4-4-Cl the preparation of the pure crystalline thiazole (**8e**) was not possible. The purification of the mixture of the products by column chromatography results in the formation of the thiazolo[5,4-*c*]pyridine (**9e**). This product was also obtained when the mixture was heated with acetic acid. In the same manner (heating in acetic acid) the thiazole (**8d**) was converted into the thiazolo[5,4-*c*]pyridine (**9d**). The formation of the thiazolopyridines (**9d,e**) was checked by an HMBC-NMR spectrum of **9d**. The detection of a cross peak of the proton at the C2´ (8.00 ppm) with the peak of the C4 (150.96 ppm) indicated the presence of the thiazolopyridine (according to ACD-calculations[20] the peak of this C-atom should be expected near to 130 ppm in the case of the isomeric thiazolopyrane).
With Ar = C_6H_4-2-OH the course of the cyclization of the intermediate (**10**) is determined by the phenolic hydroxyl group yielding the benzoxazine (**11a**) as the final product.
In a first trial the thiazolopyridine (**9d**) was tested for its inhibiting properties on the TNF-α-

production after stimulation with lipopolysaccharides in monocytes. In concentrations from 25 to 250 mM an inhibition of 36-70 % was measured.[19]



9	Ar
d	C_6H_5
e	C_6H_4-4-Cl

8	CX	Ar
a	CN	C_6H_5
b	COOMe	"
c	COMe	"
d	COC_6H_5	"
[e	COC_6H_5	C_6H_4-4-Cl]
f	COC_6H_4-4-Br	C_6H_5
g	COC_6H_4-4-CN	"
h	COC_6H_4-4-NO_2	"
i	COC_6H_4-3-NO_2	"

Scheme 3

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured with a Perkin Elmer 16 PC FTIR spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Gemini 300 operating at 300 MHz for ^{1}H and 50 MHz for ^{13}C and a Bruker DRX-600 Avance operating at 600,13 MHz and 150,91 MHz for ^{13}C. MS spectra were recorded on a JEOL JMS-D 100 spectrometer (EI, 70eV), resp. Finnigen MAT 8230.

Ethyl 3,4-Dihydro-6-methylthio-2-phenyl-4-thioxopyrimidine-5-carboxylate (5a)

A) A solution of **3a**[17] (1 mmol; 0.406 g) in 3 mL of DMSO and 0.24 mL of 5M NaOH was kept at rt for 3 d. The solution was acidified with 1N HCl. The precipitated material was filtered off and recrystallized from methanol to yield 0.25 g (82%) of **5a**. mp 163-170 ^{o}C. lit.,[17] mp 163-174 ^{o}C. IR (KBr): υ = 3140 (NH), 1725 (CO) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 306 (51, M^{+}), 104 (100).

General procedure for the formation of thiazoles (8)

A) To a stirred mixture of 5.5 mmol of HAL-CH_2-CX in 2 mL of MeOH, 5 mmol of iminothiazine hydroperchlorate (**3**),[17] and 12 mmol (1.66 mL) of Et_3N were added at 10-15^{o}C. The mixture was stirred at rt for 30 min and was then concentrated under reduced pressure. The precipitate was collected, washed with H_2O and recrystallized from methanol.

B) A solution of 1 mmol of **3** (0.406 g) in 3 mL of DMSO, 0,24 mL of 5M NaOH and 1 mmol of 4-bromoacetophenone (0.2 g) was kept at rt for 3 d. The precipitate was collected and re-crystallized from methanol.

Ethyl Cyano(5-cyano-2-phenylthiazol-4-yl)acetate (8a)

A) Starting from 0.42 g of chloroacetonitrile and 1.88 g of **3a**. Yield 1.37 g (92%). mp 120-123 ^{o}C. IR (KBr): υ = 2250 (C≡N), 2220 (C≡N), 1750 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 1.22 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 4.25 (q, 2H, J=7.1 Hz, $COO\underline{C}H_2CH_3$), 6.30 (s, 1H, C<u>H</u>), 7.57-8.01 (m, 5H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.24 ($OCH_2\underline{C}H_3$), 39.91 (<u>C</u>H(CN)$COOCH_2CH_3$), 64.65 ($O\underline{C}H_2CH_3$), 111.02, 113.01 (C≡N), 127.60-132.95 (C-5, C-phenyl), 153.95 (C-4), 162.27 (C-2), 173.83 (<u>C</u>$OOCH_2CH_3$). MS (EI, 70 eV): *m/z* (%) = 297 (18, M^{+}), 251 (6), 224 (100), 121 (10), 104 (32), 103 (8), 95 (10), 77 (10). Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C 60.59, H 3.73, N 14.13, S 10.78; Found: C 60.42, H 3.77, N 13.81, S 10.98.

Ethyl Cyano[(5-methoxycarbonyl)-2-phenylthiazol-4-yl]acetate (8b)

A) Starting from 0.84 g of methyl bromoacetate and 1.88 g of **3a**. Yield 1.41 g (85%). mp 115-118 ^{o}C. IR (KBr): υ = 2250 (C≡N), 1750 (C=O), 1710 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.21 (t, 3H, J=7.1 Hz, COOCH$_2$C<u>H</u>$_3$), 3.89 (s, 3H, COOC<u>H</u>$_3$), 4.23 (q, 2H, J=7.1 Hz, COOC<u>H</u>$_2$-CH$_3$), 6.37 (s, 1H, C<u>H</u>), 7.60-8.02 (m, 5H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.01 (OCH$_2$<u>C</u>H$_3$), 39.03 (<u>C</u>H(CN)COOCH$_2$CH$_3$), 52.83 (COO<u>C</u>H$_3$), 63.52 (O<u>C</u>H$_2$CH$_3$), 114.07 (C≡N), 124.66 (C-5), 126.72-132.23 (C-phenyl), 150.76 (C-4), 161.51 (<u>C</u>OOCH$_3$), 163.41 (C-2), 171.80 (<u>C</u>OO-CH$_2$CH$_3$). MS (EI, 70 eV): *m/z* (%) = 330 (12, M$^+$), 284 (10), 258 (100), 257 (55), 226 (83), 121 (8), 104 (55), 103 (7), 95 (44), 77 (16). Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C 58.17, H 4.27, N 8.48, S 9.71; Found: C 58.54, H 4.02, N 8.19, S 9.86.

Ethyl Cyano(5-acetyl-2-phenylthiazol-4-yl)acetate (8c)

A) Starting from 0.51 g of chloroacetone and 1.88 g of **3a**. Yield 1.52 g (97%). mp 106-111 ^{o}C. IR (KBr): υ = 2230 (C≡N), 1750 (C=O), 1710 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.19 (t, 3H, J=7.1 Hz, COOCH$_2$C<u>H</u>$_3$), 2.63 (s, 3H, COC<u>H</u>$_3$), 4.22 (q, 2H, J=7.1 Hz, COOC<u>H</u>$_2$CH$_3$), 6.29 (s, 1H, C<u>H</u>), 7.60-8.06 (m, 5H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 13.77 (OCH$_2$<u>C</u>H$_3$), 30.56 (CO-<u>C</u>H$_3$), 39.46 (<u>C</u>H(CN)COOCH$_2$CH$_3$), 62.69 (O<u>C</u>H$_2$CH$_3$), 114.63 (C≡N), 132.11 (C-5), 126.69-131.40, 132.22 (C-phenyl), 148.74 (C-4), 163.40 (C-2), 169.37 (<u>C</u>OOCH$_2$CH$_3$), 189.66 (<u>C</u>O-CH$_3$). MS (EI, 70 eV): *m/z* (%) = 314 (68, M$^+$), 268 (41), 242 (100), 241 (100), 199 (57), 121 (17), 104 (80), 103 (10), 95 (50), 77 (22). Anal. Calcd for $C_{16}H_{14}N_2SO_3$: C 61.13, H 4.49, N 8.91, S 10.20; Found: C 60.96, H 4.65, N 8.66, S 9.91.

Ethyl Cyano(5-benzoyl-2-phenylthiazol-4-yl)acetate (8d)

A) Starting from 1.1 g of phenacyl bromide and 1.88 g of **3a**. Yield 1.66 g (88%). B) Yield 0.23 g (61%). mp 105-107 ^{o}C. IR (KBr): υ = 2260 (C≡N), 1750 (C=O), 1650 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.19 (t, 3H, J=7.2 Hz, COOCH$_2$C<u>H</u>$_3$), 4.24 (q, 2H, J=7.2 Hz, COOC<u>H</u>$_2$CH$_3$), 6.27 (s, 1H, C<u>H</u>), 7.56-8.06 (m, 10H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 13.81 (OCH$_2$<u>C</u>H$_3$), 39.95 (<u>C</u>H(CN)COOCH$_2$CH$_3$), 62.78 (O<u>C</u>H$_2$CH$_3$), 114.94 (C≡N), 126.78 (C-5), 128.78-133.66 (C-phenyl). 150.61 (C-4), 163.53 (C-2), 170.36 (<u>C</u>OOCH$_2$CH$_3$), 186.32 (<u>C</u>OC$_6$H$_4$). MS (EI, 70 eV): *m/z* (%) = 376 (12, M$^+$), 330 (10), 304 (43), 303 (23), 289,6* (1, 330^2/376=289,6), 199 (6), 121 (17), 105 (100), 104 (17), 103 (14), 95 (17), 77 (100). Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C 67.00,

H 4.28, N 7.44, S 8.52; Found: C 67.25, H 4.38, N 7.20, S 8.73.

Ethyl Cyano[5-(4-bromobenzoyl)-2-phenylthiazol-4-yl]acetate (8f)

A) Starting from 1.52 g of 4-bromophenacyl bromide and 1.88 g of **3a**. Yield 1.34 g (59%). mp 132-134 ^{o}C. IR (KBr): υ = 2250 (C≡N), 1750 (C=O), 1650 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.19 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 4.23 (q, 2H, J=7.1 Hz, $COO\underline{C}H_2CH_3$), 6.24 (s, 1H, C<u>H</u>), 7.57-8.06 (m, 9H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 3.81 ($OCH_2\underline{C}H_3$), 39.53 (<u>C</u>H(CN)$COOCH_2$-CH_3), 62.82 ($O\underline{C}H_2CH_3$), 114.87 (C≡N), 126.78 (C-5), 127.72-132.18 (C-phenyl), 150.71 (C-4), 163.49 (C-2), 170.48 ($\underline{C}OOCH_2CH_3$), 185.45 ($\underline{C}OC_6H_4$). MS (EI, 70 eV): *m/z* (%) = 454 (82, M^+), 408 (63), 355 (72), 302 (75), 183 (100), 121 (84). Anal. Calcd for $C_{21}H_{15}N_2O_3BrS$: C 55.39, H 3.32, N 6.15, S 7.04; Found: C 54.97, 3.58, N 6.00, S 7.35.

Ethyl Cyano[5-(4-cyanobenzoyl)-2-phenylthiazol-4-yl]acetate (8g)

A) Starting from 1.23 g of 4-cyanophenacyl bromide and 1.88 g of **3a**. Yield 1.40 g (70%). mp 171-175 ^{o}C. IR (KBr): υ = 2250 (C≡N), 2245 (C≡N), 1750 (C=O), 1660 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.36 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 4.36 (q, 2H, J=7.1 Hz, $COO\underline{C}H_2CH_3$), 5.91 (s, 1H, C<u>H</u>), 7.48-8.03 (m, 9H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.06 ($OCH_2\underline{C}H_3$), 39.90 (<u>C</u>H(CN)$COOCH_2CH_3$), 63.73 ($O\underline{C}H_2CH_3$), 116.70, 117.62 (C≡N), 127.72-132.18 (C-5)(C-phenyl), 152.23 (C-4), 163.19 (C-2), 172.33 ($\underline{C}OOCH_2CH_3$), 185.55 ($\underline{C}OC_6H_4$). MS (EI, 70 eV): *m/z* (%) = 401 (100, M^+), 355 (72), 329 (18), 328 (18), 274,39* (1, 300^2/328=274,39), 197 (67), 130 (24), 121 (70), 104 (67), 103 (33), 102 (99), 95 (5), 80.03* (1, 102^2/130=80.03). Anal. Calcd for $C_{22}H_{15}N_3O_3S$: C 65.82, H 3.77, N 10.47, S 7.99; Found: C 65.73, H 4.04, N 10.26, S 8.16.

Ethyl Cyano[5-(4-nitrobenzoyl)-2-phenylthiazol-4-yl]acetate (8h)

A) Starting from 1.34 g of 4-nitrophenacyl bromide and 1.88 g of **3a**. Yield 1.65 g (78%). mp 157-158 ^{o}C. IR (KBr): υ = 2250 (C≡N), 1750 (C=O), 1630 cm^{-1} (C=O). ^{1}H NMR (DMSO-*d*$_6$): δ = 1.37 (t, 3H, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 4.37 (q, 2H, J=7.2 Hz, $COO\underline{C}H_2CH_3$), 5.92 (s, 1H, C<u>H</u>), 7.48-8.41 (m, 9H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.52 ($OCH_2\underline{C}H_3$), 40.38 (<u>C</u>H(CN)COO-CH_2CH_3), 64.21 ($O\underline{C}H_2CH_3$), 114.37 (C≡N), 124.47 (C-5), 127.74-150.79 (C-phenyl), 152.81 (C-4), 163.62 (C-2), 172.93 ($\underline{C}OOCH_2CH_3$), 185.82 ($\underline{C}OC_6H_4$). MS (EI-HRMS): *m/z* (%) =

421.06802 (100, M^+)($C_{21}H_{15}N_3O_5S$ requires 421.07332), 375.03255 (82, $[M-C_2H_5OH]^+$) ($C_{19}H_9N_3O_4$ requires 375.03147), 349.04017 (32), 322.03271 (78), 302.05916 (80) ,19.01281 (14), 171.01389 (23), 150.01562 (87)($C_7H_4NO_3$ requires 150.01913), 121. 01345 (76)(C_7H_5S requires 121.0111), 104.03639 (78), 76.0331 (25). Anal. Calcd for $C_{21}H_{15}N_3O_5S$: C 59.85, H 3.59, N 9.97, S 7.61; Found: C 59.89, H 3.89, N 9.93, S 7.80.

Ethyl Cyano[5-(3-nitrobenzoyl)-2-phenylthiazol-4-yl]acetate (8i)

A) Starting from 1.34 g of 3-nitrophenacyl bromide and 1.88 g of **3a**. Yield 1.45 g (69%). mp 161-165 ^oC. IR (KBr): υ = 2260 (C≡N), 1750 (C=O), 1650 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ = 1.37 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 4.37 (q, 2H, J=7.1 Hz, $COO\underline{C}H_2CH_3$), 5.91 (s, 1H, C<u>H</u>), 7.47-8.77 (m, 9H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.08 ($OCH_2\underline{C}H_3$), 39.96 (<u>C</u>H(CN)COO-CH_2CH_3), 63.75 ($O\underline{C}H_2CH_3$), 113.96 (C≡N), 123.70 (C-5), 127.34-140.13, 152.42 (C-phenyl), 148.27 (C-4), 163.20 (C-2), 172.35 (<u>C</u>$OOCH_2CH_3$), 184.67 (<u>C</u>OC_6H_4). MS (EI, 70 eV): *m/z* (%) = 421 (90, M^+), 375 (100), 348 (23), 347 (28), 320 (64), 302 (43), 199 (13), 150 (61), 121 (32), 104 (79), 93 (36), 76 (55). Anal. Calcd for $C_{21}H_{15}N_3O_5S$: C 59.85, H 3.59, N 9.97, S 7.61; Found: C 59.48, H 3.66, N 9.68, S 7.87.

Ethyl 2,4-Diphenyl-6-oxo-5,6-dihydrothiazolo[5,4-*c*]pyridine-7-carboxylate (9d)

1 mmol (0.376 g) of **8d** was added to 1 mL of acetic acid. The mixture was refluxed for 10 min. After cooling to rt the precipitate was collected. Yield 0.28 g (74%); mp 185-210 ^oC (CH_3COOH). IR (KBr): υ = 1720, 1630 cm^{-1} (C=O). ^1H NMR (DMSO-d_6,H,H-COSY): δ = 1.37 (t, 3H, J=7.2 Hz, CH_3), 4.41 (q, 2H, J=7.2 Hz, CH_2), 7.57 (s, 2H, C-4´), 7.58 (s, 2H, CH-3´´,5´´), 7.60 (s, 2H, CH-3´,5´), 7.65 (s, 1H, CH-4´´), 8.00 (s, 2H, CH-2´,6´), 8.12 (s, 2H, CH-2´´,6´´), 11.86 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, ATP, HMQC, HMBC): δ = 14.25 (CH_3)(-), 61.16 (CH_2)(+), 106.59 (C-7)(+), 120.12 (C-3a)(+), 127.84, 127.94 (C-2´´,6´´,2´,6´)(-), 129.59, 129.05 (C-3´´,5´´,3´,5´)(-), 130.37 (C-4´)(-),131.82, 137.27 (C-1´´,1´)(+), 132.92 (C-4´´)(-), 150.96 (C-4)(+), 159.60 (C-6)(+), 160.07 (C-7a)(+), 165.17 (COO)(+), 174.97 (C-2)(+), DMSO (δ = 39.52)(+). MS (EI, 70 eV): *m/z* (%) = 376 (12, M^+), 331 (51), 330 (90), 304 (61), 227 (45), 199 (47), 171 (48), 121 (48), 105 (65), 104 (41). Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C 67.00, H 4.28, N 7.44, S 8.52; Found: C 66.91, H 4.18, N 7.61, S 8.55.

Ethyl 2-(4-Chlorophenyl)-4-phenyl-6-oxo-5,6-dihydrothiazolo[5,4-*c*]pyridine-7-carboxylate (9e)

A) General procedure for the formation of thiazoles (**8**) (A), starting from 0.22 g (1.1 mmol) of phenacyl bromide, 0.44 g (1 mmol) of **3b**,[17] 2.4 mmol (0.33 mL) of Et_3N and 0.4 mL of MeOH. The oily precipitate was purified by PLC (Merck, PLC plates 20x20 cm, silica gel 60 F254, 2 mm)(dioxane/toluoene=1:4). Yield 0.34 g (83%). B) General procedure for the formation of thiazoles (**8**)(A), starting from 1.1 g (5.5 mmol) of phenacyl bromide, 2.3 g (5 mmol) of **3b**, 12 mmol (1.66 mL) of Et_3N and 2 mL of MeOH. The oily precipitate was washed with H_2O and treated with 5 mL of acetic acid. The mixture was refluxed for 10 min. After cooling to rt, the precipitate was collected. Yield 1.6 g (78 %). mp 205-218 ^oC (C_6H_5Cl). IR (KBr): υ = 1730, 1630 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ = 1.57 (t, 3H, J=7.2 Hz, CH_3), 4.58 (q, 2H, J=7.2 Hz, CH_2), 7.26-8.10 (m, 10H, phenyl), 12.36 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 14.65 (CH_3), 62.95 (CH_2), 99.88, 123.67 (C-3a, C-7), 129.06-139.21 (C-phenyl), 166.50 (COO), 156.62, 161.25, 170.58, 174.97 (C-2,4,6,7a). MS (EI, 70 eV): *m/z* (%) = 410 (100, M^+), 365 (81), 364 (55), 338 (87), 227 (37), 199 (32), 171 (42), 155 (24), 139 (28), 138 (14). Anal. Calcd for $C_{21}H_{15}N_2O_3ClS$: C 61.39, H 3.68, N 6.82, Cl 8.63, S 7.80; Found: C 61.31, H 3.78, N 6.58, Cl 8.87, S 7.57.

Ethyl Cyano[(4-benzoylmethylthio)-*2H*-1,3-benzoxazin-2-ylidene]acetate (11a)

General procedure for the formation of thiazoles (**8**) (A), starting from 0.22 g (1.1 mmol) of phenacyl bromide, 0.42 g (1 mmol) of **3c**,[16] 2.4 mmol (0.33 mL) of Et_3N, 0.4 mL of MeOH. The oily precipitate was purified by PLC (Merck, PLC plates 20x20 cm, silica gel 60 F254. 2 mm) (dioxane/toluoene=1:4). Yield 0.24 g (61%). mp 162-163 ^oC (EtOH). IR (KBr): υ = 2214 (C≡N), 1713 (C=O), 1685 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 1.37 t, 1,41 t (3H, J=10.40 Hz, $COO-CH_2C\underline{C}H_3$), 4.28 q, 4.35 q (2H, J=10.40 Hz, $COO\underline{C}H_2CH_3$), 5.12 (s, 2H, SCH_2CO), 7.29-8.17 (m, 9H, phenyl). ^{13}C NMR ($CDCl_3$): δ = 14.47 ($OCH_2\underline{C}H_3$), 39.85 (SCH_2), 61.02 ($O\underline{C}H_2CH_3$), 78.55 ($\underline{C}(CN)COOCH_2CH_3$), 117.41-137.16 (C≡N, C-aromat), 151.41, 162.89, 164.09 (C-8a, $\underline{C}OOCH_2CH_3$, C-2), 174.34 (C-4), 192.15 ($\underline{C}OC_6H_5$). MS (EI, 70 eV): *m/z* (%) = 392 (82, M^+), 366 (14), 347 (15), 105 (100). Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C 64.27, H 4.11, N 7.14, S 8.17; Found: C 64.28, H 4.23, N 7.44, S 8.24.

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