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# Reaction of Aminothiazole-oximetosylates with Thiols

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***Abstract*** - The reaction of ethyl 2-(2-aminothiazol-4-yl)-2-tosyloxyiminoacetate and its tritylamino analogue with thiols gave ethyl 2-(5-R-thio-2-amino- or tritylamino-thiazol-4-yl)-2-oxoacetate derivatives. Structures were elucidated by ir, $^{1}H$-, $^{13}C$-nmr and mass spectroscopy. A reaction mechanism is suggested.

Several stable oximetosylates are reported in the literature which react with thiols, e.g. α-(*p*-toluenesulfonyloxyimino)benzylcyanide and ethyl 2-phenyl-*p*-toluenesulfonyloxyiminoacetate undergo a Beckmann type rearrangement upon the action of thiols.[1,2a] Later this assumption was corrected by the authors who established the sulfenylimine structure of the product.[3] Similarly, sulfenylimines are formed in the reaction of other α-tosyloxyiminonitriles and thiols.[4] However, thiols containing an active methylene group form the corresponding cyclic 4-aminoizothiazole derivatives.

Similarly, 4-aminoisothiazole derivatives were produced[5] from substituted α-(*p*-toluenesulfonyl-oxyimino)benzylcyanide, and 4-hydroxyisothiazole derivatives from ethyl 2-phenyl-*p*-toluenesulfonyl-oxyiminoacetate by reacting them with methyl thioglycolate. Isothiazoles are also formed from analogues carrying a pyridyl or thienyl moiety instead of the phenyl group.

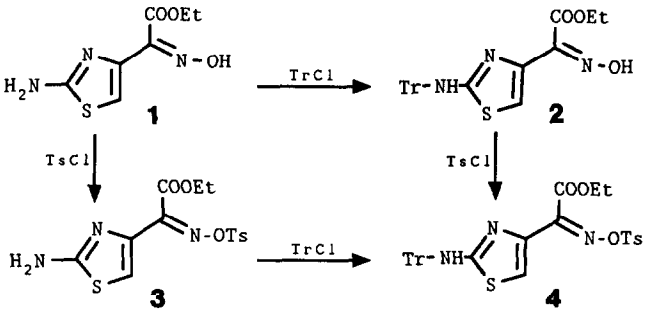
In the present paper the reaction of some aminothiazole-oximetosylate derivatives with thiols is reported.

Preparation of starting materials

Compounds **1** and **2**, used as starting materials for the synthesis of oximetosylates,[6,7] have several nucleophilic centers (i.e. the oxygen and the nitrogen[8] of the oxime, the 2-amino group of the thiazole, and the nitrogen of the hetero ring) and each of them may react with an electrophilic reagent.

Reaction of **2** and TsCl afforded **4** in high yield and no nitrone was formed as a by-product. Though, the reaction of the unprotected 2-amino group of **1** could be assumed, the 2-amino-oximetosylate **3** was obtained on tosylation in 90 % yield, and neither the 2-tosylamino-oxime, nor the

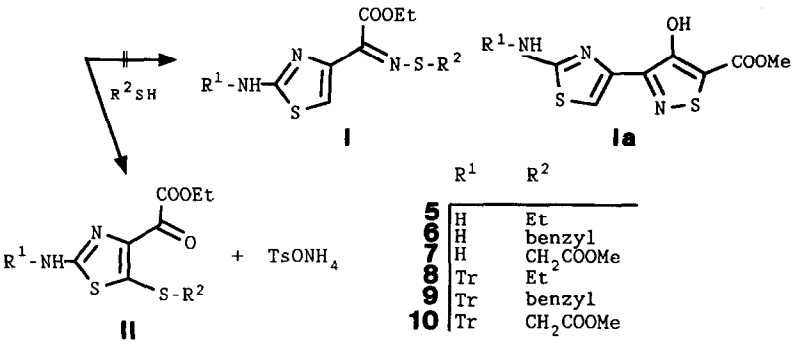
2-aminonitrone or the ditosylated product were detectable (Scheme 1). The stucture of **3** was confirmed chemically too, as tritylation afforded **4**.




Scheme 1

Reaction with thiols

Reactions of **3** and **4** with ethanethiol, benzylmercaptane or methyl thioglycolate in the presence of triethylamine, led only to decomposition products. When the reaction was performed in the presence of a small amount of water, and in the absence of any base, instead of the expected **I** or in the case of methyl thioglycolate, **Ia**, a new product was formed, besides ammonium toluenesulfonate.




Scheme 2

In the reactions of various thiols with either **3** or **4** (Scheme 2) in a variety of solvents (THF, acetone, ether) type **II** products (**5** to **10**) were obtained (yields 40-60 %) without exception in addition to ammonium toluenesulfonate.

Structure elucidation

Ir, $^1$H-nmr and $^{13}$C-nmr data of the new compounds as well as those of the oxo-precursor (**11**), of the known oxime **1**,[9] used as starting material, and those of the *N*-acetyl derivative (**12**) are

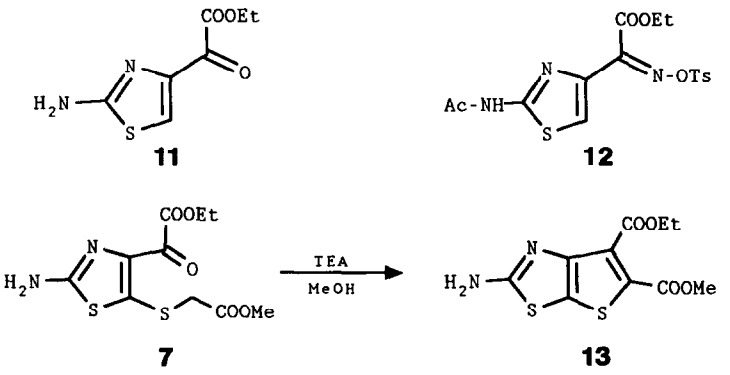
presented in Table 1. No specific comments are required for their role in structure elucidation thus only the following short remarks are made.

The H-5 signals of the thiazole ring of *Z*-tosyloxime esters* **3** and **4** appear at 6.8 ppm, the C-5 $^{13}$C-nmr line in the upfield part of the aromatic range, at 115.5 and 113.8 ppm, resp.

The carbon resonance lines of the oxime group are observed at 139.5 and 138.6 ppm, resp. The tertiary character of the C-5 atom is indicated also by its higher line intensity in the $^{13}$C-nmr spectrum, prepared with 90° pulse, and was confirmed by the DEPT spectrum of compound **3**.

The respective signals are also detectable in the spectra of **11** and **12**, though with a downfield shift of both H-5 and C-5 lines, which is considerably higher in the case of **11** due to the stronger *-I* effect of the carbonyl substituent replacing the oxime group, and to a smaller extent in the spectrum of **12**, in agreement with the weaker electronwithdrawing effect of the 2-acetamido group. The downfield shift of H-5 in **11** is especially large (ca. 1.15 ppm) due to the cumulative influence of the *-I* as well as the anisotropic effect of the neighbouring carbonyl group. The carbon line of the $\alpha$-ketone group in compound **11** is shifted downfield by about 50 ppm, compared to the respective line of the oxime esters, and is recorded in the predicted range,[10a] at 180.4 ppm.

The H-5 line is absent in the $^{1}$H-nmr spectra of SR$^{2}$-substituted products **5** to **10**, and the substituted (quaternary) character of the C-5 atom is unambiguously confirmed by the proton-coupled C-nmr spectra of **7** and **10**. An about 23 ppm downfield shift is induced on the C-5 line by the cumulative effects of the S-substituent on the one hand and that of the $\alpha$-oxo-substituent replacing the oxime ester group on the other. The C-4 line is shifted upfield by about 10.5 ppm compared to oxime esters **3** and **4** (due to the *+I* effect of the thioether substituent[10b]) while the line of the ester carbonyl carbon is shifted downfield by about 4 ppm (due to the *-I* effect of the $\alpha$-keto group[10c]). The chemical shift of the ketone carbonyl (C$\alpha$) is in the 180.5 ± 1.3 ppm range. Compared to the starting compouns **3** and **4**, as well as to model compounds **11** and **12**, the above spectral data unambiguously prove type **II** structures for compounds **5** to **10**.




Scheme 3

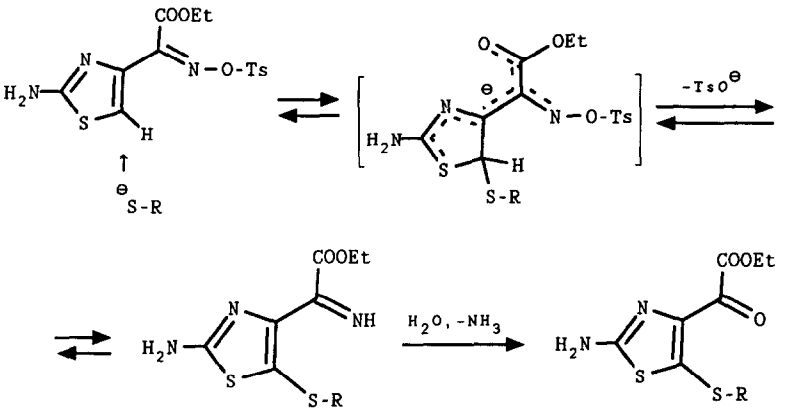
*Proof of the *Z*-configuration is the H-5 shift around 6.8 ppm as the corresponding signal of the *E*-isomer would be at 7.50 ppm.[8]

In accordance with the type **II** structure the high resolution mass spectrum of compound **5** gave a molecular ion of molecular mass 260 with an intensity of 37 %. By the loss of a carbethoxy radical ion *m/z* 187 a peak of 100 % intensity is formed. Loss of $C_2H_4$ and CO from this ion yields fragment ions $C_4H_3N_2OS_2$ and $C_5H_7N_2S_2$, giving a doublet at *m/z* 159. The third most intense peak (14 %) is the fragment ion *m/z* 127 which may be deduced from the base peak by hydrogen rearrangement and loss of $CH_3CHS$.

Chemically the type **II** structure was proved (Scheme 3) by converting compound **7** in methanol, in the presence of triethylamine by heating into the thieno[3.2-*d*]thiazole derivative **13**. This ring system is known but the process for its preparation is new.[11]

Proposed mechanism for the formation of compounds **5** to **10**

It is known[12] that the C atoms of the thiazole ring have a decreasing order of electrophilic and nucleophilic reactivities, respectively, i.e. 5 > 2 > 4 and 2 > 5 > 4. In derivatives **3** and **4** however, the C-5 atom of the thiazole becomes electron deficient because of the *-I* effect of the oximetosylate group, promoting a nucleophilic attack at the C-5 atom. Thus an anionic $\sigma$-adduct is formed *via* the attack of the thiolate anion at C-5. In the conjugated system formed the negative charge is distributed as shown in Scheme 4. Subsequently, proton transfer and loss of $OTs^-$ lead to the imine which undergoes acid catalysed hydrolysis[2b] via the immonium cation.




Scheme 4

Thiol and water, one molecule of each, are participating in the reaction yielding one molecule of ammonium toluenesulfonate which precipitates from the aprotic solvent shifting the equilibrium towards the products.

Thus the reaction can be considered as the conjugate addition of a nucleophile to an $\alpha,\beta$-unsaturated oximetosylate (the $\alpha,\beta$-unsaturated system is part of a heteroaromatic ring) and subsequent elimination of TsOH.

So far only one example hase been described in the literature where an oximtosylate attached to a benzofurane ring undergoes analogous nucleophilic attack in $\beta$ position.[13]

The first part of the proposed mechanism, up to the imino ester formation, is somewhat similar to the VNS (Vicarious Nucleophilic Substitution of Hydrogen) theory of M. Makosza,[14] except that in our case the leaving group (TsO) is not placed on the nucleophile but on the substrate molecule. Accordingly, it may be considered as an extension of the VNS theory.

## EXPERIMENTAL

IR spectra were run in KBr pellets on a Bruker IFS-113v FT-spectrometer equipped with an Aspect 2000 computer and a vacuum optical system.

The $^{1}H$- and $^{13}C$-nmr spectra were recorded in $CDCl_3$ solution in 5 or 10 mm tubes at room temperature, on Bruker WM-250 ($^{1}H$, $^{13}C$) and/or WP-80SY ($^{13}C$) FT-spectrometers controlled by Aspect 2000 computer at 250.13 ($^{1}H$) and 62.89 or 20.14 MHz ($^{13}C$), with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectral width 5 and 15 or 5 kHz, pulse width 1 and 5 or 3.5 $\mu$s ($\sim 20°$ and $\sim 30°$ flip angle), acquisition time 1.64 and 1.02 or 1.64 s, number of scans 16 or 32 ($^{1}H$) and 0.5-5 K ($^{13}C$), computer memory 16 and 32 or 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening: 0.7 and 1.0 or 2.0 Hz) and for the $^{13}C$-nmr spectra complete proton noise decoupling ($\sim 3$ or $\sim 1.5$ W) were applied.

DEPT spectra were run in a standard way, using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, $90°$ pulse widths 10.8 and 22.8 $\mu$s for $^{13}C$ and $^{1}H$, respectively. The estimated value for $J(C,H)$ resulted in a 3.7 ms delay for polarization.

Melting points are uncorrected. All yields are preparative ones.

*Ethyl 2-(2-aminothiazol-4-yl)-2-p-tosyloxyiminoacetate* (**3**)

To a stirred mixture of 16.1 g (75 mmol) of **1**[6] and 12 ml (85.7 mmol) of triethylamine (TEA) in 750 ml of acetone, 15.8 g (83 mmol) of *p*-tosyl chloride (TsCl) was added at -5 °C. After stirring for 2.5 h at RT, the solid material was filtered. The filtrate was diluted with water (2.5 l). The precipitated material was filtered, washed with water, diisopropyl ether and methanol, yield 25.2 g of **3**.

*Ethyl 2-(2-tritylaminothiazol-4-yl)-2-p-tosyloxyiminoacetate* (**4**)

Method A:

To a stirred mixture of 16.5 g (35 mmol) of **2**[7] and 11.5 ml (82 mmol) of TEA in 175 ml of tetrahydrofuran (THF), 14.75 g (77 mmol) of TsCl was added at -20° C. After stirring for 3.5 h at RT, the solid material was filtered. The filtrate was evaporated at reduced pressure. The residue was worked-up with water, extracted 3 times with ether, dried with $MgSO_4$ and evaporated. Crystallization of the residue from hexane and washing with methanol gave 20.2 g of **4**.

Method B:

To a stirred solution of **3** (1.7 g. 4.6 mmol) and TEA (0.78 ml, 5.6 mmol) in 10 ml of THF, trityl chloride (1.58 g, 5.6 mmol) was added at -20° C. After ten minutes stirring was continued for 4 h without cooling. The reaction mixture was poured into 100 ml of water and extracted 3 times with ether.

Table. 1. Characteristic ir-frequencies (in KBr pellets, $cm^{-1}$), $^1H$- and $^{13}C$-nmr data ($\delta_{TMS}$ = 0 ppm) for compounds **3-13** in $CDCl_3$ solution[a] at 250 ($^1H$) and 63 MHz ($^{13}C$).[b]

| Com- | ir | | $^1H$-nmr | | | $^{13}C$-nmr[f] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | νC=O | $CH_3$(Et) | $CH_2$(Et) | CH/$CH_2$ | $NH/NH_2$ | thiazole ring | | | ester group | | | $C_\alpha$ | $CH_2$ | $CH_3$[g] |
| pound | ester | t[c](3H) | qa(2H) | s(1H)[d] | broad[e] | C-2 | C-4 | C-5 | $CH_3$ | $CH_2$ | C=O | (Pos.4) | ($R_2$) | ($R_2$) |
| **3** | 1738 | 1.38 | 4.42 | 6.78 | 7.3 | 170.2 | 152.8 | 115.4 | 14.1 | 63.1 | 160.2 | 139.5 | - | 21.8 |
| **4** | 1745 | 1.35 | 4.39 | 6.80[h] | 6.8[h] | 167.9 | 153.6 | 113.8 | 13.8 | 62.3 | 160.1 | 138.6 | - | 21.3 |
| **5** | 1740[i] | 1.38[j] | 4.37 | 2.95 | 5.8 | 164.8[k] | 142.0[l] | 140.3[l] | 14.0[h] | 62.0 | 164.6[k] | 179.2 | 31.9 | 14.0[h] |
| **6** | 1725 | 1.37 | 4.36 | 4.11 | 5.7 | 165.2 | 143.1 | 138.1 | 14.0 | 62.2 | 164.5 | 179.3 | 42.1 | - |
| **7** | 1726 | 1.29 | 4.30 | 4.02 | 7.45 | 167.5 | 142.6 | 138.2 | 15.8 | 63.3 | 166.4 | 181.7 | 39.8 | 54.5 |
| **8** | 1745 | 1.36 | 4.35 | 2.67 | 6.7 | 165.0[k] | 141.8 | 138.3 | 13.9[l] | 61.7 | 164.7[k] | 180.0 | 31.5 | 13.8[l] |
| **9** | 1740 | 1.35 | 4.34 | 3.85 | 6.7 | 165.5[k] | 142.7 | 136.3 | 13.9 | 61.9 | 164.5[k] | 179.9 | 41.8 | - |
| **10** | 1730 | 1.37 | 4.32 | 3.45 | 6.8 | 166.3 | 143.8 | 133.1 | 14.0 | 62.2 | 164.4 | 180.0 | 39.0 | 52.7 |
| **11** | 1730 | 1.30 | 4.33 | 7.94 | 7.55 | 170.4 | 148.0 | 124.8 | 15.5 | 63.5 | 165.5 | 180.4 | - | - |
| **12** | 1744 | 1.38 | 4.45 | 7.42 | 10.6 | 159.7[k] | 153.0 | 118.9 | 14.1 | 63.1 | 160.2[k] | 138.5 | - | 21.7 |
| **13** | 1718 | 1.30 | 4.32 | - | 7.65 | 174.0 | 129.9[k] | 155.5 | 15.9 | 63.4 | 166.0 | 130.1[m] | 129.5[m] | 54.3 |

Further signals - Ir-bands νNH: 1-3 broad maxima between 3450 and 3100, 3300-2800 diffuse band (**12**); νC=O (ester, $R_2$): 1726 (**7**, together with the band of the COOEt-group), 1717 (**10**); νC=O (ketone): 1637 (**5**), 1655 (**6**), 1640 (**7**), 1620 (**8**), 1660 (**9**), 1640 (**10**), 1655 (**11**); amide-I: 1697 (**12**), $\nu_{as}SO_2$: 1375 (**3**), 1366 (**4**), 1383 (**12**), $\nu_sSO_2$ (splitted band pair, **3**, **4**, **12**): 1195 ± 3 and 1180 ± 1, $\nu_{as}$C-O (ester): 1255-1285 (second band for **13** at 1240); $\nu_s$C-O (ester): 1020-1070 (two bands for **13**); $\gamma C_{Ar}H$: 825 ± 4 (Ts, **3**, **4**, **12**), 750-770 (Ph in **6**, **9**, two bands for trityl groups in **4**, **8-10**); $\gamma C_{Ar}C_{Ar}$: 695-710 (Ph + trityl).

$^1$H-nmr signals $CH_3$(SEt), t (3H): 1.16 (**8**), $CH_3$(Ac), s(3H): 2.09 (**12**), $OCH_3$, s(3H): 3.70 (**7**), 3.61 (**10**), 3.81 (**13**). Tosyl (**3**, **4**, **12**): $CH_3$, s(3H): 2.40 ± 0.02; ArH-2,6: 7.82 ± 0.03, ArH-3,5: 7.30 (**3**, **4**), 7.22 (**12**); Trityl (**4**, **8-10**) and S-benzyl (**6**, **9**): ArH: ~7.3 m (15H, 5H for **6** and 20H for **9**);

$^{13}$C-nmr lines; $CH_3$(Ac): 23.0 (**12**), Trityl (**4**, **8-10**): $C_{quat}$: 72.0 ± 0.2, C-1: 143.0 ± 0.2, C-2,6 and C-3,5: 128.0, 128.9 (**4**), 128.4, 129.2 (**8**, **10**), 128.3,[h] 129.1 (**9**), C-4: 127.7 ± 0.2; Tosyl: C-1: 145.7 (**3**, **12**), 145.0 (**4**), C-2,6: 129.9 (**3**, **12**), 129.4 (**4**), C-3,5: 128.6 (**3**, **4**), 129.0 (**12**), C-4: 132.1 ± 0.1; S-benzyl: C-1:135.3 (**6**), 135.7 (**9**), C-2,6: 129.2 (**6**), 128.3,[h] (**9**), C-3,5: 128.7, C-4: 128.0 (**6**), 127.7[n] (**9**), C=O (COOMe): 170.7 (**7**), 168.4 (**10**), 162.9 (**13**), C=O(Ac): 168.6 (**12**).

[a] Solvent: DMSO-$d_6$ for **7**, **11**, **13**; [b] Measuring frequency: 20 MHz ($^{13}$C) for **5**, **9**, **11**, **12**; [c] $^3J(CH_3,CH_2)$: 7.1 Hz; [d] Multiplicity is qa for **5** and **8**, intensity: 2H for **5-10**; [e] Intensity: 2H for **3**, **5-7**, **11**, **13**, 1H for **4**, **8-10**, **12**; [f] Assignments were proved by proton-coupled spectra for **3**, **7**, **10**, **13** and also by DEPT for **3**; [g] Tosyl (**3**, **4**, **12**), ethyl in $R_2$ (**5**, **8**), carbomethoxy (**7**, **10** and **13**); [h] Overlapping signals; [i] Splitted band pair with the second maximum at 1720 $cm^{-1}$; [j] Intensity: 6H; [k,l] Interchangeable lines; [m] The lines[k] of COOMe/Et-substituted carbons in thiophene ring; [n] In overlap with the C-4 line of the trityl group.

The combined extracts were washed with water, dried over $MgSO_4$ and evaporated. The residue was crystallized from diisopropyl ether, filtered, giving 0.8 g of starting material. The filtrate was placed into a refrigerator for 24 h. The precipitated crystals were filtered and washed with diisopropyl ether. Yield 0.3 g of **4**.

Table 2. Physical data for compounds **3 - 13**

| Com-pound | M.p. °C | Empirical formula | M.W. | Yield % | Elemental analysis, % Calculated / Found C | H | N |
|---|---|---|---|---|---|---|---|
| 3[a] | 124-126 | $C_{14}H_{15}N_3O_5S_2$ | 369.42 | 91 | 45.52/45.37 | 4.09/3.99 | 11.37/11.15 |
| 4[b] | 136-138 | $C_{33}H_{29}N_3O_5S_2$ | 611.74 | 94 | 64.79/64.69 | 4.78/4.67 | 6.87/ 6.83 |
| 5[c] | 122-123 | $C_9H_{12}N_2O_3S_2$ | 260.34 | 42 | 41.52/41.27 | 4.65/4.56 | 10.76/10.64 |
| 6[c] | 129-131 | $C_{14}H_{14}N_2O_3S_2$ | 322.41 | 41 | 52.16/51.92 | 4.38/4.19 | 8.69/ 8.79 |
| 7[d] | 157-158 | $C_{10}H_{12}N_2O_5S_2$ | 304.35 | 64 | 39.47/39.48 | 3.97/3.91 | 9.20/ 9.17 |
| 8[d] | 116-117 | $C_{28}H_{26}N_2O_3S_2$ | 502.66 | 40.5 | 66.91/67.01 | 5.21/5.29 | 5.57/ 5.57 |
| 9[d] | 169-171 | $C_{33}H_{28}N_2O_3S_2$ | 567.73 | 41 | 70.19/70.15 | 5.00/5.06 | 4.96/ 4.96 |
| 10[d] | 166-168 | $C_{29}H_{26}N_2O_5S_2$ | 546.67 | 62 | 63.72/63.65 | 4.79/4.78 | 5.12/ 5.13 |
| 11[e] | 147-149 | $C_7H_8N_2O_3S$ | 232.27 | 45 | 36.20/36.05 | 3.47/3.41 | 12.06/12.15 |
| 12[d] | 170-172 | $C_{16}H_{17}N_3O_6S_2$ | 411.45 | 85 | 46.71/46.50 | 4.16/3.93 | 10.21/ 9.89 |
| 13[f] | 184-186 | $C_{10}H_{10}N_2O_4S_2$ | 286.33 | 93 | 41.95/41.70 | 3.52/3.49 | 9.78/10.06 |

[a] From acetone; [b] Method A; [c] The crude product was dissolved in ether, and the pH was adjusted to 2 by 2 M methanolic HCl. The solid was collected by filtration, washed with ether and acetone, suspended in 2% $NaHCO_3$ solution and extracted 3 times with ether, dried over $MgSO_4$ and evaporated. The residue was stirred with diisopropyl ether, filtered and recrystallized from methanol; [d] From methanol; [e] Ref. [9]; [f] From 1,2-Dichloroethane

*Ethyl 2-(5-substituted-thio-2-aminothiazol-4-yl)-2-oxoacetate* (**5-7**)

General method:

To a stirred solution of **3** (1.5 g, 4 mmol) in 15 ml of THF and 0.3 ml of water, the thiol (10 mmol) was added. After 24 h stirring at RT, the reaction mixture was filtered and the filtrate was evaporated. The residue was triturated with hexane and water, finally recrystallized from methanol.

*Ethyl 2-(5-substituted-thio-2-tritylaminothiazol-4-yl)-2-oxoacetate* (**8-10**)

General method:

To a stirred solution of **4** (1.2 g, 2 mmol) in 10 ml of ether and 0.2 ml of water, the thiol (5 mmol) was added. After 24 h stirring at RT, the reaction mixture was filtered and the filtrate was evaporated. The residue was triturated with diisopropyl ether and water, then washed with warm methanol.

*Ethyl 2-(2-acetylaminothiazol-4-yl)-2-p-tosyloxyiminoacetate* (**12**)

A mixture of 25 g (75 mmol) of **3** and 125 ml of acetic anhydride was stirred for 8 h. The mixture was diluted with 500 ml water and placed into a refrigerator. The precipitated material was filtered, washed with water and ether, yield 23.7 g of **12**.

*2-Amino-2-methoxycarbonyl-6-ethoxycarbonyl-thieno[3,2-d]thiazole* (**13**)

A stirred solution of **7** (0.9 g, 3 mmol) and TEA (0.42 ml, 3 mmol) in 10 ml of methanol was refluxed for 15 min. After cooling the reaction mixture was poured into 100 ml of water and stirred for another 15 min. The precipitated crystalline material was filtered, washed with water and diisopropyl ether, yielding 0.79 g of **13**.

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