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Isothiazoles. Part 14: New 3-aminosubstituted isothiazole dioxides and their mono- and dihalogeno derivatives

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Abstract—3-Alkylamino- and 3-arylamino isothiazole dioxides unsubstituted at C-4 and C-5 were synthesized starting from dithiopropionic amides. Taking advantage of the direct chlorination during the cyclization process or realizing an addition–elimination process with bromine on the final 3-aminoisothiazole dioxide derivatives, the corresponding 5-chloro-, 4,5-dichloro- or the 4-bromoisothiazole dioxides could also be made available.

1. Introduction

The reactivity of 3-amino-4-arylisothiazole 1,1-dioxides has been studied by us over the last few years and several synthetic approaches allowing the preparation of a number of 5-substituted-3-dialkylamino-4-aryl-isothiazole 1,1-dioxides and 5-substituted-3-dialkylamino-4-aryl-4,5-dihydroisothiazole 1,1-dioxides have been developed.[1–4] Some representatives of this class showed a promising antiproliferative effect presumably through inhibition of protein prenylation.[5,6] Furthermore, a number of them has been identified as inhibitors of *Trypanosoma brucei* protein farnesyltransferase in preference to the mammalian enzyme.[7] These results prompted us in continuing our research: it is known that inhibitors of *T. brucei* protein farnesyltransferase are not only able to arrest the growth of cultured parasites, which are the causative agent of African sleeping sickness, but a number of protein farnesyltransferase inhibitors are well developed as pharmaceutically active agents which are now in clinical development for the treatment of cancer.[8–10] Aiming to obtain compounds with high efficacy and specificity and to clarify the role of the substituents in the interaction with the bioreceptorial site, we designed the synthesis of new derivatives of 3-amino-isothiazole dioxides with two major features: (i) a primary or secondary amine at C-3 able to act as a donor in an hydrogen bond with the receptor site (ii) unsubstituted both at C-4 and C-5. Furthermore, we evaluated the possibility of preparing 3-amino-isothiazole dioxides halogenated on the ring on C-4, or on C-5 or on both carbons. These new classes of compounds are very attractive as key starting materials for the synthesis of a variety of isothiazole dioxide derivatives, as well as PFT inhibitors themselves. As reported above, only isothiazole *S*,*S*-dioxides substituted with an aryl group on C-4 and a dialkylamine on C-3 were synthesized up to now and the halogenation of such a system makes available only the 5-bromoderivative.[2] The methods developed by us for these compounds are not applicable for the synthesis of the new designed isothiazole dioxides. In this paper, we describe an efficient synthetic route to these products.

2. Results and discussion

It has been reported that cyclization of dithiodipropionic amides afford *N*-substituted isothiazolones which could be transformed into 3-aminoisothiazoles by reacting with $POCl_3$ and an excess of ammonia.[11–13] Taking into account our interest in synthesizing a variety of 3-aminoisothiazoles, we tried to generalize the method by using several different amines (only aniline or simple alkylamines having been used before). Accordingly, we performed the reaction using alkylamines (such as **3a**–**d**) and aniline **3e**, but also with several substituted benzylamines (**f**, **g**, **h**) and biologically interesting amines such as aminoacids (glycine **3i**, phenylalanine **3l**). In fact, according to the methodology, we reacted the acyl chloride **2**, immediately after the formation from **1**, with the appropriate amine **3a**–**l**. Compounds **4a**–**l**, easily obtained in all cases, were dissolved in dichloroethane and cyclized to isothiazolones **5** with SO_2Cl_2 at 10–15°C. The reaction mixture also contained a variable amount of 5-chloro and 4,5-dichloro derivatives **6** and **7**. As already observed the ratio of **5**, **6**, **7** could be influenced in

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Table 1. Effects of experimental conditions on **5**, **6**, **7** ratio

Compounds	Method A[a] yields (%)	Method B[b] yields (%)	Compounds	Method A yields (%)	Method B yields (%)	Compounds	Method A yields (%)	Method B yields (%)
5a[11]	46	0	**6a**[11]	25	18	**7a**[11]	0	30
5b[11]	56	44	**6b**[11]	18	34	**7b**[11]	0	8
5c[11]	51	0	**6c**[11]	44	31	**7c**	0	42
5e[11]	60	50	**6e**[14]	0	37	**7e**	0	0
5i	30	0	**6i**	0	0	**7i**	0	35

[a] **4**/SO_2Cl_2 ratio: 1:3; 2 h; 10°C.
[b] **4**/SO_2Cl_2 ratio: 1:6; 12–24 h; 25–35°C.

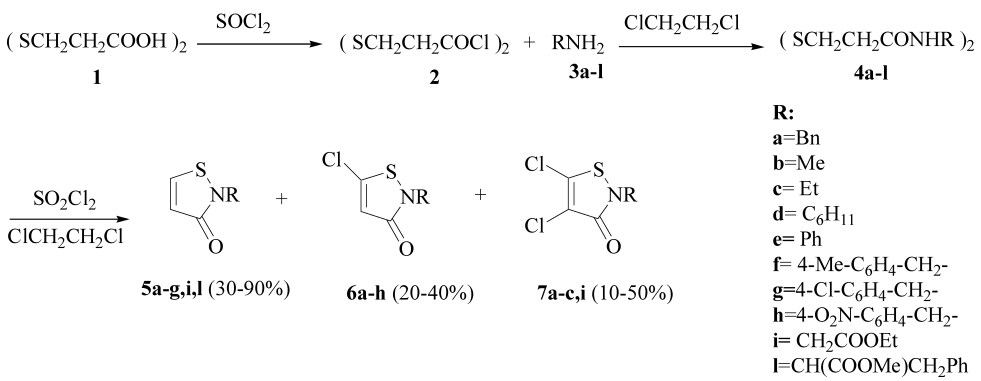
part by using a higher molar ratio of SO_2Cl_2/amide and by increasing temperature and time.[11] Also, the solubility of the dithiopropionic amide in the reaction solvent is somewhat important: in the case of **4h**, which has a very low solubility in dichloroethane, only the 5-chloro derivative **6h** could be obtained and the use of co-solvent favouring the dissolution (i.e. methanol, ethylacetate) only had the effect of lowering the yield of **6**. The results of these two methods are summarized in Table 1 (Scheme 1).

Isothiazolones **5a–g,i,l** were then reacted with $POCl_3$ followed by NH_3 to afford the 3-amino derivatives **8**. We found that the same reaction was also effective in the case of the 5-chloro derivatives **6** and the 4,5-dichloro derivatives **7** which afforded with $POCl_3$ the corresponding quaternary chloro compounds. By subsequent nucleophilic attack of ammonia on the sulfur atom, an open chain *S*-amino intermediate was formed which could be easily cyclized to 3-aminoisothiazoles **9** and **10**. Isothiazole dioxides **11**, **12** and **13** were obtained using 2 equiv. of *m*-chloroperbenzoic acid in dichloromethane or methanol (Scheme 2).

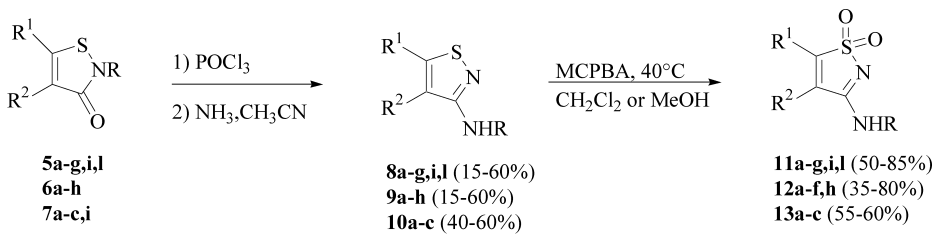
The ^{1}H NMR spectra of **11** are mainly characterized by two doublets associated with H-4 and H-5 in the range of 6.9–7.0 and 7.8–7.9, respectively. A singlet at 6.25–6.35 associated with H-4 is the main feature for compounds **12**. The 5-proton absorption is evidently shifted on sulfur oxidation while a minor effect was exerted on the 4-proton. The method described above allows the synthesis of 5-chloro- or 4,5-dichloro derivatives but the 4-chloroisothiazoles could not be obtained except as a contaminant. Also, the attempt to chlorinate directly the isothiazole system was not successful because it was not possible to stop chlorination at the monochloro stage even under mild conditions, as already reported.[14] On this basis, with the aim to selectively synthesize a 4-halogeno derivative, we turned our attention to the direct bromination of the 3-aminoisothiazole dioxide, taking into consideration that the position 4 in the isothiazole system is prone to electrophilic attack.[14,15] Accordingly, compound **11a** was reacted with an equimolecular amount of bromine at room temperature affording compound **14**. The ^{1}H NMR spectrum is characterized by two doublets (5.55, 5.68 δ; J=4.0 Hz) clearly associated with H-4 and H-5 indicating the addition of bromine to the double bond. By treating **14** with an equimolecular amount of a base (TEA) or by simple refluxing in CCl_4, HBr elimination and formation of 4-bromoisothiazole dioxide **15** was observed (Scheme 3).

It is evident that bromination of the isothiazole dioxide system is an electrophilic addition followed by an elimination reaction, in contrast to the bromination of the isothiazole system which occurs via electrophilic substitution. This is not surprising, taking into account that oxidation to the sulfur atom results in a reduction of the aromatic character of the system and, from a formal point of view, the system could be considered more appropriately as a cyclic unsaturated *N*-sulfonylamidine.[16] In line with this is the result of the dehydrobromination of **14** which afforded the 4-bromo derivative **15** and not the 5-bromo derivative. Confirmation was obtained by performing semiempirical and ab-initio calculations. As shown in Scheme 4 we considered the reaction paths, respectively, leading to 5-bromo (path A) and 4-bromo (path B) derivatives. In order to save computational time, calculations were performed on the *N*-methyl derivative.

Our aim was to compare the stability of the anionic intermediates B and C, respectively, deriving from deprotonation at C-5 and C-4. As reported in Table 2, AM1 energies at this level show that the **C** intermediate is 1.78 Kcal more stable than **B**, confirming the experimental



Scheme 1.



5a-g,i,l
6a-h
7a-c,i

8a-g,i,l (15-60%)
9a-h (15-60%)
10a-c (40-60%)

11a-g,i,l (50-85%)
12a-f,h (35-80%)
13a-c (55-60%)

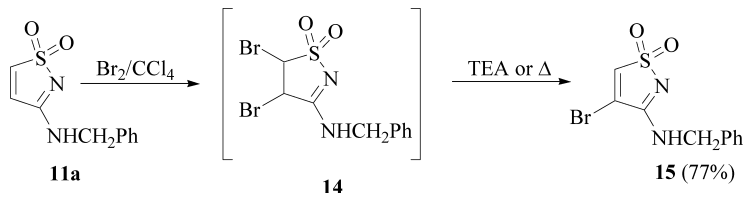
Compd.	R	R^1	R^2	Compd.	R	R^1	R^2
5,8,11a	C_6H_5-CH_2	H	H	**6,9,12c**	Et	Cl	H
5,8,11b	Me	H	H	**6,9,12d**	C_6H_{11}	Cl	H
5,8,11c	Et	H	H	**6,9,12e**	Ph	Cl	H
5,8,11d	C_6H_{11}	H	H	**6,9,12f**	4-Me-C_6H_4-CH_2	Cl	H
5,8,11e	Ph	H	H	**6,9g**	4-Cl-C_6H_4-CH_2	Cl	H
5,8,11f	4-Me-C_6H_4-CH_2	H	H	**6,9,12h**	4-NO_2-C_6H_4-CH_2	Cl	H
5,8,11g	4-Cl-C_6H_4-CH_2	H	H	**7,10a**	C_6H_5-CH_2	Cl	Cl
5,8,11i	CH_2COOEt	H	H	**7,10,13b**	Me	Cl	Cl
5,8,11l	$CH(COOMe)CH_2Ph$	H	H	**7,10,13c**	Et	Cl	Cl
6,9,12a	C_6H_5-CH_2	Cl	H	**7i**	CH_2COOEt	Cl	Cl
6,9,12b	Me	Cl	H				

Scheme 2.

synthetic results. As shown in Figure 1, optimized geometries of compounds **B** and **C** show that respectively, carbons C-5 and C-4 assume both a sp^2 hybridisation, suggesting that the negative charge is delocalized directly on the SO_2 group for the **B** intermediate and on the *N*-sulfonylamidine moiety for the **C** intermediate.

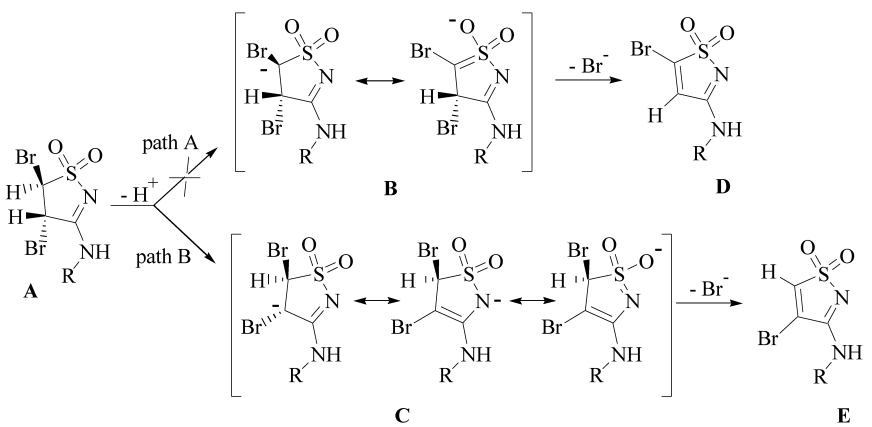
In order to confirm the semiempirical results, structures **A**, **B**, **C**, **D** and **E** were reoptimized at the ab-initio HF/6-31++G(d,p) level. Surprisingly, while geometry **C** readly converged to a minimum, we did not achieve convergence for structure **B**, neither as a minimum nor as a transition state. Several unsuccessful trials were made, but the only way by which we succeeded in achieving convergence was by constraining the C4–Br bond distance.

As shown in Figure 2, carbon C-5 in the constrained-optimized structure **B** maintains sp^3 hybridisation, while



11a **14** **15** (77%)

Scheme 3.



A **B** **C** **D** **E**

Scheme 4.

Table 2. AM1 and HF total (a.u.) and relative (Kcal/mol) energies of intermediate structures **B** and **C**

Structure	AM1		HF/6-31++G(d,p)	
	E_{tot} (a.u.)	E_{rel} (Kcal/mol)	E_{tot} (a.u.)	E_{rel} (Kcal/mol)
B	−93.263897140	1.776	−5950.3590727487	17.762[a]
C	−93.266727235	0	−5950.3873791529	0

[a] Energy value obtained by an energy calculation on the C4-Br constrained distance optimized geometry.

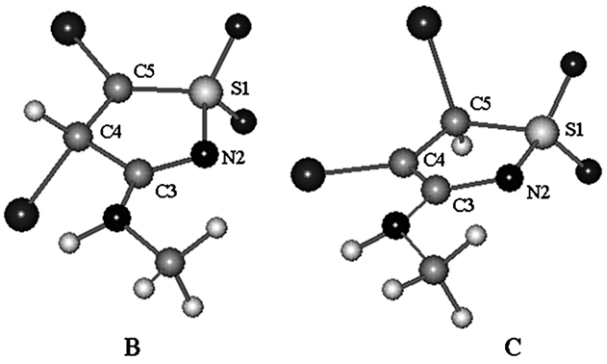


Figure 1. AM1 optimized geometries of intermediates **B** and **C**. Improper torsion angles (deg.) for structure **B**: C5–Br–S1–C4=−0.40; C4–Br–C5–C3=38.36; improper torsion angles (deg.) for structure **C**: C5–Br–S1–C4=−32.47; C4–Br–C5–C3=−0.73.

carbon C-4 in structure **C** is nearly planar and the C3–C4 distance suggests the presence of a π bond.

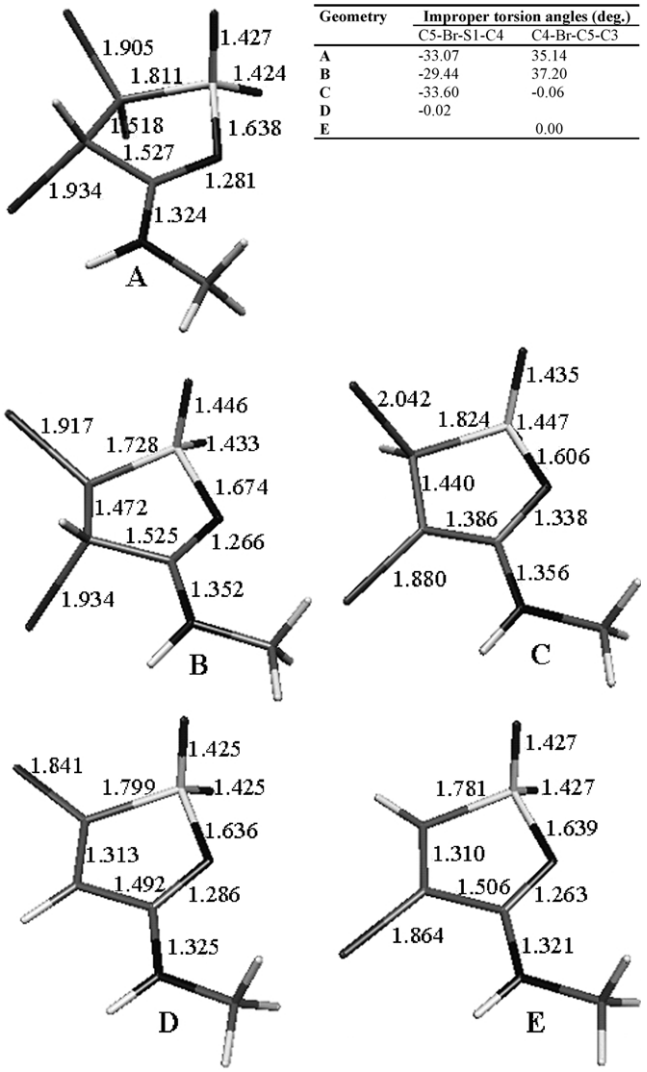
Furthermore, electron density maps of the highest occupied molecular orbital reported in Figure 3 show an intense accumulation of electronic density localized on **B** C-5, while electronic density in **C** is well delocalized on the sulfonylamidine nitrogen as represented by the mesomeric forms depicted in Scheme 4. This behavior thus confirms that the SO_2 group does not directly delocalize the negative charge which is instead well delocalized by the *N*-sulfonylamidine moiety.

3. Conclusions

In summary, here is described a simple pathway allowing the synthesis of 3-alkyl- and 3-arylamino-isothiazole dioxides **11** unsubstituted at C-4 and C-5 and of the corresponding 5-chloro-, 4,5-dichloro- and 4-bromo derivatives **12**, **13** and **15**. 3-Aminoisothiazoles **11**, **12**, **13** and **15** could represent key intermediates for the synthesis of a number of isothiazole dioxides of pharmacological interest. Further work in this direction will be published in due course.

4. Experimental

^{1}H NMR spectra were obtained in $CDCl_3$ as the solvents (except when indicated) with Bruker AC 200, Bruker Avance 300 and Varian Gemini 200 instruments. Coupling constants (*J*) are given in Hertz. Melting points were determined using a Büchi 510 (capillary) or an Electrothermal 9100 apparatus. IR spectra were recorded on a Jasco IR report 100 spectrophotometer. Mass spectra were obtained by electron impact ionisation at 70 eV from a



Geometry	Improper torsion angles (deg.)	
	C5-Br-S1-C4	C4-Br-C5-C3
A	-33.07	35.14
B	-29.44	37.20
C	-33.60	-0.06
D	-0.02	
E		0.00

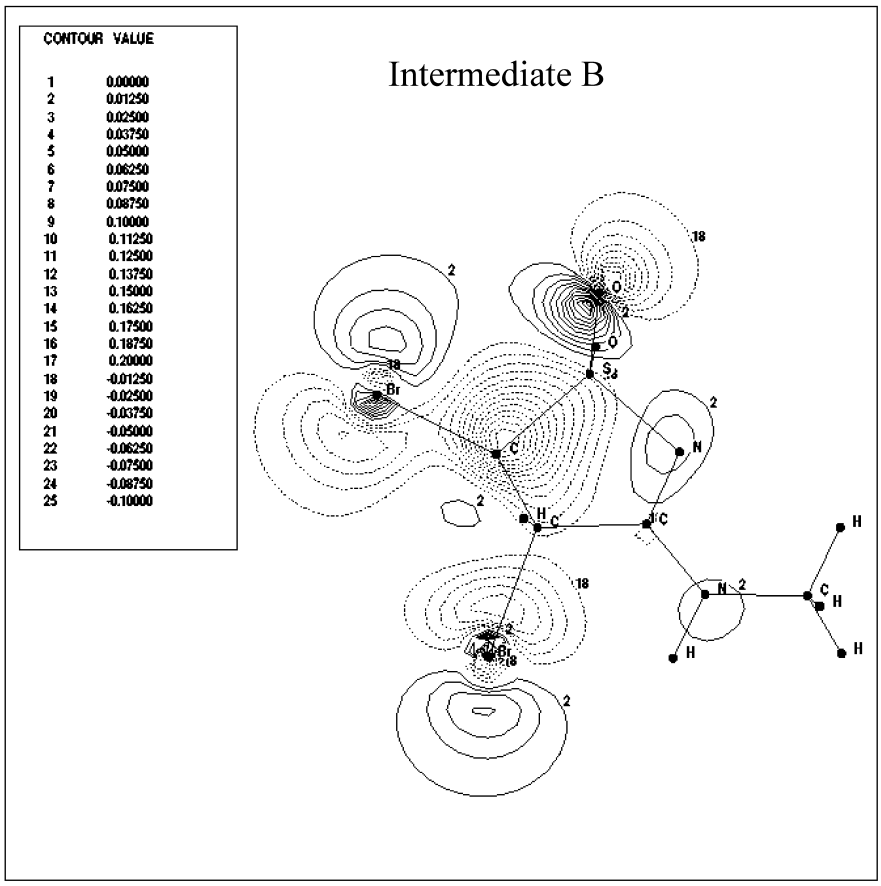
Figure 2. HF/6-31++G(d,p) optimized geometries for **A**, **C**, **D**, **E** and constrained-optimized geometry for **B**. Selected bond lengths are expressed in Å.

Finnigan INCOS 50 or from a Finnigan MD 800 instruments using the direct exposure probe (DEP).

The dithiopropionamides starting material **4a–g** were prepared by aminolysis of dithiopropionyl chloride **2** or of the corresponding methyl ester.[11,12] **5a–g**; **6a–c,e**; **7a–b**; **8a–e** are known compounds.[11–13]

4.1. Quantum chemical calculations

Geometries were fully optimized at AM1 level to a gradient



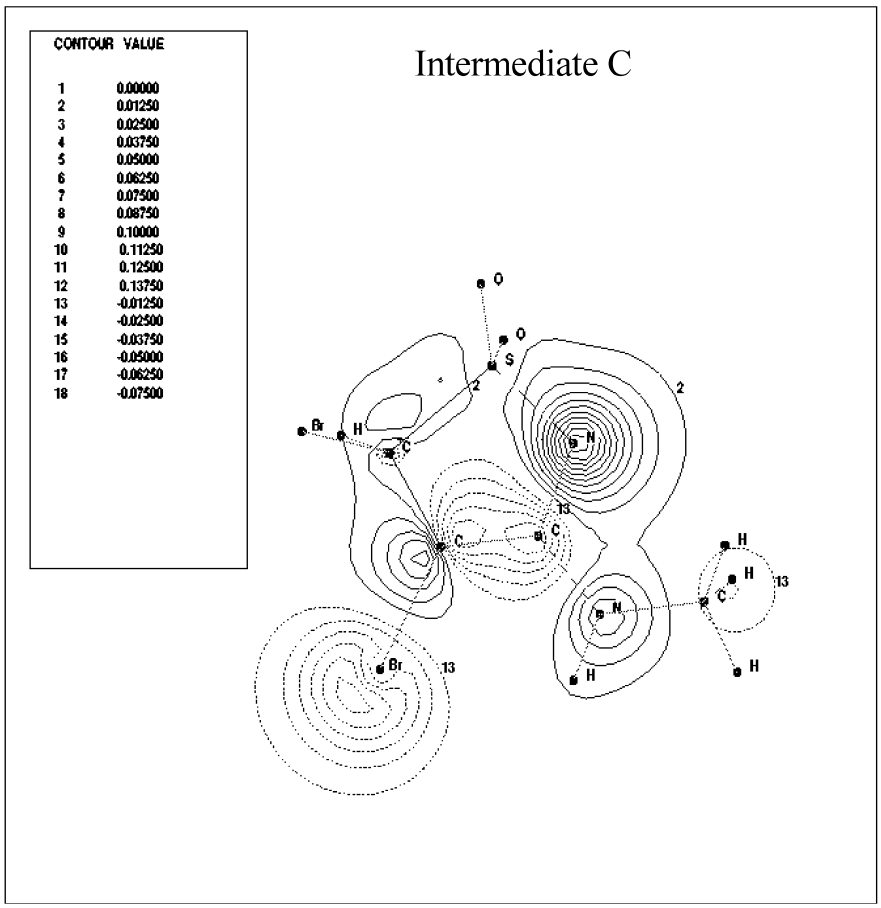


Figure 3. HF/6-31++G(d,p) electron density maps for constrained-optimized geometry **B** and for optimized geometry **C**.

of 0.001 using the program Hyperchem6.03 on a PIII PC running Windows 2000.[17] In order to better include electron correlation AM1 single point energies were than calculated with configuration interaction microstate option considering an orbital criterion of 3 occupied and 3 unoccupied orbitals.[18] Ab-initio calculations were performed using the program Gamess on a HP64000 cluster.[19] Pople style split valence basis set HF/6-31++G(d,p) was used for all ab-initio calculations; diffuse functions has been included for more accuracy, as the molecules possess several lone pairs of electrons.[20,21] Linear dependence threshold (QMTTOL) was set at 1×10^{-7}, HONDO/Rys integrals were used for all integrals (INTTYP=HONDO) and DIIS converger was used instead that SOSCF. Analytical frequency calculations have been performed on all stationary points in order to caracterize a minimum (no imaginary frequencies) or a transition state (one imaginary frequency). Graphics has been generated with Molekel version 4.3 for Linux, electron density maps has been generated with Molden version 3.7 for Linux.[22,23]

4.2. General procedure for the preparation of dithiopropionamides 4h–l

82.6 mmol of the amine chloridrate **3h–l** and TEA (14.74 mL, 204 mmol) were suspended under vigorous stirring in anhidrous dichloroethane (132 mL). A solution of freshly prepared **2** (6 g, 24.29 mmol) in dichloromethane (20 mL) was slowly dropped into the suspension maintaining the temperature between 5 and 15°C. Stirring was continued at the same temperature until disappearance of the starting material (TLC: AcOEt 100%, about 4 h). Water (50 mL) was added under vigorous stirring and the mixture transferred to a separatory funnel. The organic layer was separated and washed again with water (2×50 mL). The organic phase was dried with Na_2SO_4, filtered and evaporated to dryness affording **4h–l** as solids which were recrystallized from diethyl ether.

4.2.1. *N*-4-Nitrobenzyl-3-(4-nitrobenzylcarbamoyl-ethyldisulfanyl)-propionamide 4h. Yield 79%. Mp 130°C (light brown powder from Et_2O). IR 3298 (NH), 1642 cm^{-1} (CO). ^1H NMR (DMSO-d_6) 2.60 (t, 2H, J=7 Hz, CH_2), 2.96 (t, 2H, J=7 Hz, CH_2), 4.41 (d, 2H, J=6 Hz, CH_2NH), 7.42 (d, 2H, J=8.8 Hz, arylH), 8.18 (d, 2H, J=8.8 Hz, arylH), 8.62 (bs, 1H, NH). ^{13}C NMR 34.5, 35.6 (CH_2), 42.4 ($ArCH_2$), 124.1, 128.8 (arCH), 147.1, 148.3 (arC), 171.1 (CO). Calcd for $C_{20}H_{22}N_4O_6S_2$ (478.54) C 50.20 H 4.63 N 11.71, found C 50.34 H 4.90 N 11.50.

4.2.2. 3-[2-(Methoxycarbonylmethyl-carbamoyl)-ethyldisulfanyl]propionylamino acetic acid methyl ester 4i. Yield 88%. Mp 118°C (white powder from Et_2O). IR 3306 (NH), 1747, 1646 (CO) cm^{-1}. ^1H NMR 1.30 (t, 3H, J=7 Hz, CH_3), 2.69 (t, 2H, J=7 Hz, CH_2), 3.01 (t, 2H, J=7 Hz, CH_2), 4.07 (d, 2H, J=5 Hz, CH_2NH), 4.23 (q, 2H, J=7 Hz, CH_2), 6.55 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6) 14.7 (CH_3), 34.4, 35.4, 41.4 (CH_2), 61.1 (OCH_2), 170.5, 171.3 (CO). Calcd for $C_{14}H_{24}N_2O_6S_2$ (380.48) C 44.19 H 6.36 N 7.36, found C 44.45 H 6.40 N 7.21.

4.2.3. 2-[3-[2-(1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-ethyldisulfanyl]propionylamino]-3-phenyl-propionic acid methyl ester 4l. Yield 95%. Mp 88–90°C (white powder from Et_2O). IR 3329 (NH), 1743, 1641 (CO) cm^{-1}. ^1H NMR (DMSO-d_6) 2.50 (t, 2H, J=7 Hz, CH_2), 2.82–3.07 (m, 4H, CH_2), 3.59 (s, 3H, CH_3), 4.46 (m, 1H, CH), 7.16–7.31 (m, 5H, arylH), 8.43 (bs, 1H, NH). ^{13}C NMR 34.2, 35.3 (CH_2), 38.8 ($PhCH_2$), 52.5, 54.3 (CH+OCH_3), 127.3, 128.9 129.7 (arCH), 137.8 (arC), 171.1, 172.7 (CO). Calcd for $C_{26}H_{32}N_2O_6S_2$ (532.67) C 58.62 H 6.06 N 5.26, found C 58.75 H 6.10 N 5.11.

4.3. General procedure for the preparation of isothiazolones 5, 6, 7 from 4[11]

Method A. The dithiopropionamide **4** (25 mmol) was suspended in anhydrous dichloroethane and stirred at 0°C in a ice bath. A solution of SO_2Cl_2 (10.12 g, 75 mmol) in dichloroethane (10 mL) was slowly dropped into the suspension. After 2 h at 10°C the reagent was usually completely dissolved giving a clear solution. Solvent was evaporated under reduced pressure and the residue taken up with dichloromethane (50 mL) and washed twice with water (15 mL each). The organic layer was separated, dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography (AcOEt/cyclohexane 0:100 to 100:0) affording pure **5**, **6**, **7**.

Method B. The same reaction was performed with higher amount of SO_2Cl_2 (150 mmol) stirring the solution overnight at room temperature affording, after elaboration (see above), **5**, **6**, **7**. In the case of compounds **4a**,**b**,**c**,**e**,**i**, both methods were used for comparing the yields (see Table 1).

4.3.1. Ethyl (3-oxoisothiazol-2(3*H*)-yl)acetate 5i. Yield 30%. Colourless oil. IR 3298 (NH), 1743, 1642 (CO) cm^{-1}. ^1H NMR 1.31 (t, 3H, J=7 Hz, CH_3), 4.25 (q, 2H, J=7 Hz, CH_2), 4.53 (s, 2H, CH_2), 6.30 (d, 1H, J=6.2 Hz, H-4), 8.18 (d, 1H, J=6.2 Hz, H-5). ^{13}C NMR 14.3 (CH_3), 44.5 (NCH_2), 62.2 (OCH_2), 113.6 (C-4), 141.1 (C-5), 167.9, 171.1 (C-3+COO). Calcd for $C_7H_9NO_3S$ (187.22) C 44.91 H 4.85 N 7.48, found C 44.72 H 4.90 N 7.22.

4.3.2. Methyl 2-(3-oxoisothiazol-2(3*H*)-yl)-3-phenylpropanoate 5l. Yield 30%. Colourless oil. IR 3274 (NH), 1735, 1642 (CO) cm^{-1}. ^1H NMR 3.00–3.50 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 5.54 (m, 1H, CH), 6.18 (d, 1H, J=6.2 Hz, H-4), 7.11–7.36 (m, 5H, arylH), 8.08 (d, 1H, J=6.2 Hz, H-5). ^{13}C NMR 38.3 (CH_2), 56.8, 53.0 (CH+OCH_3), 113.7, 128.8–129.5 (arCH), 141.0 (C-5), 169.3, 170.6, 172.3. Calcd for $C_{13}H_{13}NO_3S$ (263.31) C 59.30 H 4.98 N 5.32, found C 59.65 H 5.02 N 5.13.

4.3.3. 5-Chloro-2-cyclohexylisothiazol-3(2*H*)-one 6d. Yield 40%. Mp 77–80°C (white powder from Et_2O). IR 1669 (CO) ^1H NMR 1.12–2.08 (m, 10H, CH_2), 4.37–4.50 (m, 1H, CH), 6.25 (s, 1H, H-4). ^{13}C NMR 25.3, 25.7, 30.4 (CH_2), 53.9 (CH), 115.2 (C-4), 146.3 (C-5), 166.8 (C-3). Calcd for $C_9H_{12}ClNOS$ (217.72) C 49.65 H 5.56 N 6.43, found C 49.82 H 5.65 N 6.13.

4.3.4. 5-Chloro-2-(4-methylbenzyl)-isothiazol-3(2*H*)-one 6f. Yield 26%. Mp 84–87°C (Et_2O). IR 1645 (CO) cm^{-1}. ^1H NMR 2.38 (s, 3H, CH_3), 4.86 (s, 2H, CH_2), 6.30 (s, 1H, H-4), 7.20–7.23 (m, 4H, arylH). ^{13}C NMR 21.3 (CH_3), 47.3

(CH_2), 114.7 (C-4), 128.7, 129.8 (arCH), 132.6, 138.7 (ArC), 146.5 (C-5), 166.9 (C-3). Calcd for $C_{11}H_{10}ClNOS$ (239.72) C 55.11 H 4.20 N 5.84, found C 55.34 H 4.43 N 5.71.

4.3.5. 5-Chloro-2-(4-chlorobenzyl)-isothiazol-3(2*H*)-one 6g. Yield 31%. Mp 79–82°C (white powder from Et_2O). IR 1648 (CO) cm^{-1}. ^1H NMR 4.87 (s, 2H, CH_2), 6.32 (s, 1H, H-4), 7.24–7.39 (m, 4H, arylH). ^{13}C NMR 46.83 (CH_2), 114.7 (C-4), 129.4–130.0 (arCH), 134.3–134.9 (arC), 146.9 (C-5), 167.0 (C-3). Calcd for $C_{10}H_7Cl_2NOS$ (260.14) C 46.17 H 2.71 N 5.38, found C 46.34 H 2.80 N 5.21.

4.3.6. 5-Chloro-2-(4-nitrobenzyl)-isothiazol-3(2*H*)-one 6h. Yield 31%. Mp 98–100°C (white powder from Et_2O). IR 1634 (CO) cm^{-1}. ^1H NMR 5.01 (s, 2H, CH_2), 6.36 (s, 1H, H-4), 7.49 (d, 2H, J=8.8 Hz, arylH), 8.25 (d, 2H, J=8.8 Hz, arylH). ^{13}C NMR 46.5 (CH_2), 114.6 (C-4), 124.4, 129.1 (arCH), 143.0, 147.3, 148.2 (Cq), 167.1 (C-3). Calcd for $C_{10}H_7ClN_2O_3S$ (270.69) C 44.37 H 2.61 N 10.35, found C 44.50 H 2.70 N 10.05.

4.3.7. 4,5-Dichloro-2-ethylisothiazol-3(2*H*)-one 7c. Yield 42%. Light yellow oil. IR 1649 (CO) cm^{-1}. ^1H NMR 1.36 (t, 3H, J=7 Hz, CH_3), 3.89 (q, 2H, J=7 Hz, CH_2). ^{13}C NMR 14.98 (CH_3), 37.30 (CH_2), 159.00 (C-3), 144.88 (C-5), 109.80 (C-4). Calcd for $C_5H_5Cl_2NOS$ (197.08) C 30.32 H 2.54 N 7.07, found C 30.65 H 2.62 N 7.01.

4.3.8. Ethyl (4,5-dichloro-3-oxoisothiazol-2(3*H*)-yl)acetate 7i. Yield 35%. Mp 85°C (white powder from Et_2O). IR 1660, 1731 cm^{-1} (CO). ^1H NMR 1.33 (t, 3H, J=7 Hz, CH_3), 4.28 (q, 2H, J=7 Hz, CH_2), 4.55 (s, 2H, CH_2). ^{13}C NMR 14.3 (CH_3), 45.3 (CH_2), 62.6 (OCH_2), 114.6 (C-4), 140.9 (C-5), 162.5 (C-3), 167.2 (CO). Calcd for $C_7H_7Cl_2NO_3S$ (256.11) C 32.83 H 2.75 N 5.47, found C 32.95 H 2.82 N 5.32.

4.4. General procedure for the preparation of 3-aminoisothiazole 8, 9, 10

Isothiazol-3-ones **5** or **6** or **7** (8 mmol) were suspended in $POCl_3$ (15 mL) and stirred at room temperature until disappearance (TLC: AcOEt 100%, about 24 h) of the starting material (sometimes it could be useful to warm the solution in an oil bath at 100°C for 30–40 min to complete the reaction). Diisopropylether was added to the mixture and a red gum precipitated. Decantation of the solvent afforded a gum perfectly suitable for the next step. This gum was suspended in CH_3CN (40 mL) and NH_3 gas was bubbled for about 30 min under stirring at 0°C. The reaction mixture was brought to room temperature and the solvent was evaporated under reduced pressure. The residue was purificated by column chromatography (AcOEt/cyclohexane 0:100 to 100:0) affording **8** or **9** or **10**.

4.4.1. *N*-(4-Methylbenzyl)isothiazol-3-amine 8f. Yield 15%. Mp 77–79°C (white powder from Et_2O). IR 3294 (NH) cm^{-1}. ^1H NMR 2.36 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 6.45 (d, 1H, J=4.8 Hz, H-4), 7.05–7.40 (m, 4H, arylH), 8.40 (d, 1H, J=4.8 Hz, H-5). ^{13}C NMR 21.3 (CH_3), 48.8 (CH_2), 111.5 (C-4), 127.9, 129.6 (arCH), 136.3, 137.3 (arC), 147.9 (C-5), 166.1 (C-3). Calcd for $C_{11}H_{12}N_2S$ (204.29) C 64.67 H 5.92 N 13.71, found C 64.81 H 6.00 N 13.48.

4.4.2. *N*-(4-Chlorobenzyl)isothiazol-3-amine 8g. Yield 33%. Mp 93–96°C (white powder from Et_2O). IR 3300 (NH) cm^{-1}. ^1H NMR 4.57 (s, 2H, CH_2), 6.46 (d, 1H, J=4.8 Hz, H-4), 7.28–7.35 (m, 4H), 8.41 (d, 1H, J=4.8 Hz, H-5). ^{13}C NMR 47.4 (CH_2), 111.5 (C-4), 128.0, 129.0 (arCH), 133.1, 137.9 (arC), 147.9 (C-5), 165.6 (C-3). Calcd for $C_{10}H_9ClN_2S$ (224.71) C 53.45 H 4.04 N 12.47, found C 53.52 H 4.16 N 12.31; m/z 224 (M^+).

4.4.3. Ethyl (isothiazol-3-ylamino)acetate 8i. Yield 59%. Mp 59–62°C (white powder from Et_2O). IR 3352 (NH), 1727 (CO) cm^{-1}. ^1H NMR 1.20–1.40 (m, 3H, CH_3), 4.20–4.31 (m, 4H, CH_2), 5.10 (bs, 1H, NH), 6.52 (d, 1H, J=4.8 Hz, H-4), 8.40 (d, 1H, J=4.8 Hz, H-5). ^{13}C NMR 14.4 (CH_3), 45.5 (CH_2), 61.5 (CH_2O), 112.0 (C-4), 148.0 (C-5), 165.0 (C-3), 171.4 (CO). Calcd for $C_7H_{10}N_2O_2S$ (186.23) C 45.15 H 5.41 N 15.04, found C 45.23 H 5.53 N 15.00.

4.4.4. Methyl 2-(isothiazol-3-ylamino)-3-phenylpropanoate 8l. Yield 49%. Mp 110–113°C (white powder from Et_2O). IR 3407 (NH), 1747 (CO) cm^{-1}. ^1H NMR 3.15–3.35 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.84–4.94 (m, 1H, CH), 5.03 (bs, 1H, NH), 6.45 (d, 1H, J=4.8 Hz, H-4), 7.12–7.36 (m, 5H, arylH), 8.38 (d, 1H, J=4.8 Hz, H-5). ^{13}C NMR 38.5 (CH_2), 52.4, 57.2 (CH+OCH_3), 112.2 (C-4), 127.2, 128.7, 129.6 (arCH), 136.6 (arC), 147.9 (C-5), 164.3 (C-3), 173.5 (CO). Calcd for $C_{13}H_{14}N_2O_2S$ (262.33) C 59.52 H 5.38 N 10.68, found C 59.80 H 5.42 N 10.48.

4.4.5. *N*-Benzyl-5-chloroisothiazol-3-amine 9a. Yield 50%. Mp 79–80°C (white powder from Et_2O). IR 3313 (NH) cm^{-1}. ^1H NMR 4.55 (d, 2H, J=5.8 Hz, CH_2), 4.73–4.92 (bs, 1H, NH), 6.4 δ (s, 1H, H-4), 7.3–7.39 δ (m, 5H, arylH). ^{13}C NMR 47.6 (CH_2), 112.1 (C-4), 127.7, 127.8, 128.9 (arCH), 139.1 (arC), 152.1, 164.2 (C-3, C-5). Calcd for $C_{10}H_9ClN_2S$ (224.71) C 53.45 H 4.04 N 12.47, found C 53.30 H 4.07 N 12.29; m/z 224 (M^+).

4.4.6. 5-Chloro-*N*-methylisothiazol-3-amine 9b. Yield 61%. Mp 72–75°C (white powder from Et_2O). IR 3248 (NH) cm^{-1}. ^1H NMR 2.97 (s, 3H, CH_3), 4.43 (bs, 1H, NH), 6.38 δ (s, 1H, H-4). ^{13}C NMR 29.9 (CH_3), 111.8 (C-4), 151.7 (C-5), 165.1 (C-3). Calcd for $C_4H_5ClN_2S$ (148.61) C 32.33 H 3.39 N 18.85, found C 32.12 H 3.45 N 18.69.

4.4.7. 5-Chloro-*N*-ethylisothiazol-3-amine 9c. Yield 55%. Mp 63–65°C (white powder from Et_2O). IR 3282 (NH) cm^{-1}. ^1H NMR 1.25 (t, 3H, J=7 Hz, CH_3), 3.37 (m, 2H, CH_2), 4.45 (bs, 1H, NH), 6.37 (s, 1H, H-4). ^{13}C NMR 15.3 (CH_3), 38.31 (CH_2), 12.0 (C-4), 151.7 (C-5), 164.5 (C-3). Calcd for $C_5H_7ClN_2S$ (162.64) C 36.92 H 4.34 N 17.22, found C 36.80 H 4.56 N 17.56.

4.4.8. 5-Chloro-*N*-cyclohexylisothiazol-3-amine 9d. Yield 45%. Mp 88–89°C (white powder from Et_2O). IR 3243 (NH) cm^{-1}. ^1H NMR (CD_3OD) 1.19–2.04 (m, 10H, CH_2), 3.55 (m, 1H, CH), 6.46 (s, 1H, H-4). ^{13}C NMR 25.0, 25.9, 33.2 (CH_2), 51.0 (CH), 113.3 (C-4), 149.5 (C-5), 164.2 (C-3). Calcd for $C_9H_{13}ClN_2S$ (216.73) C 49.88 H 6.05 N 12.93, found C 49.76 H 6.12 N 12.75.

4.4.9. 5-Chloro-*N*-phenylisothiazol-3-amine 9e. Yield 41%. Mp 81–84°C (Et_2O). IR 3240 (NH) cm^{-1}. ^1H NMR

6.70 (s, 1H, H-4), 6.70–6.75 (bs, 1H, NH), 7.00–7.15 (m, 1H, arylH), 7.25–7.45 (m, 4H, arylH). ^{13}C NMR 113.5, 118.6, 122.8, 129.5 (arCH+C-4), 140.7 (arC), 152.4 (C-5), 160.6 (C-3). Calcd for $C_9H_7ClN_2S$ (210.68) C 51.31 H 3.35 N 13.30, found C 51.10 H 3.17 N 13.05.

4.4.10. 5-Chloro-*N*-(4-methylbenzyl)isothiazol-3-amine 9f. Yield 49%. Mp 76–79°C (white powder from Et_2O). IR 3250 (NH) cm^{-1}. ^{1}H NMR 2.36 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 4.82 (bs, 1H, NH), 6.38 (s, 1H, H-4), 7.5–7.28 (m, 4H, arylH). ^{13}C NMR 21.3 (CH_3), 47.4 (CH_2), 112.0 (C-4), 127.8, 129.6 (arCH), 135.9, 137.4 (arC), 152.0 (C-5), 164.2 (C-3). Calcd for $C_{11}H_{11}ClN_2S$ (238.74) C 55.34 H 4.64 N 11.73, found C 55.23 H 4.72 N 11.48.

4.4.11. 5-Chloro-*N*-(4-chlorobenzyl)isothiazol-3-amine 9g. Yield 15%. Mp 90°C dec. (white powder from Et_2O). IR 3287 (NH) cm^{-1}. ^{1}H NMR 4.51 (s, 2H, CH_2), 4.8–5.0 (bs, 1H, NH), 6.39 (s, 1H, H-4), 7.27–7.36 (m, 4H). ^{13}C NMR 46.8 (CH_2), 112.1 (C-4), 129.1, 129.5 (arCH), 130.0–137.1 (arC), 152.3,(C-5), 163.9 (C-3). Calcd for $C_{10}H_8Cl_2N_2S$ (259.16) C 46.35 H 3.11 N 10.81, found C 46.56 H 3.05 N 10.69.

4.4.12. 5-Chloro-*N*-(4-nitrobenzyl)isothiazol-3-amine 9h. Yield 48%. Mp 120–122°C (white powder from Et_2O). IR 3247 (NH) cm^{-1}. ^{1}H NMR 4.67 (s, 2H, J=6 Hz, CH_2), 5.00 (bs, 1H, NH), 6.43 (s, 1H, H-4), 7.54 (d, 2H, J=9 Hz, arylH), 8.22 (d, 2H, J=9 Hz, arylH). ^{13}C NMR 46.6 (CH_2), 112.1 (C-4), 124.1, 128.2 (arCH), 147.0, 147.6 (arC), 152.6 (C-5), 163.5 (C-3). Calcd for $C_{10}H_8ClN_3O_2S$ (269.71) C 44.53 H 2.99 N 15.58, found C 44.78 H 3.10 N 15.32.

4.4.13. *N*-Benzyl-4,5-dichloroisothiazol-3-amine 10a. Yield 55%. Mp 59–62°C (white powder from Et_2O). IR 3290 cm^{-1} (NH). ^{1}H NMR 5.91 (s, 2H, CH_2), 7.30–7.49 (m, 5H, arylH+1H, NH). ^{13}C NMR 48.8 (CH_2), 114.9 (C-4), 128.9, 129.1, 129.2 (arCH), 134.6 (arC), 139.4 (C-5), 162.0 (C-3). Calcd for $C_{10}H_8Cl_2N_2S$ (259.16) C 46.35 H 3.11 N 10.81, found C 46.45 H 3.15 N 10.72.

4.4.14. 4,5-Dichloro-*N*-methylisothiazol-3-amine 10b. Yield 43%. Light yellow oil. IR 3292 cm^{-1} (NH). ^{1}H NMR 3.39 (s, 3H, CH_3), 4.55 (bs, 1H, NH). ^{13}C NMR 31.5 (CH_3), 115.2 (C-4), 138.2 (C-5), 162.2 (C-3). Calcd for $C_4H_4Cl_2N_2S$ (183.06) C 26.24 H 2.20 N 15.30, found C 26.45 H 2.43 N 15.56.

4.4.15. 4,5-Dichloro-*N*-ethylisothiazol-3-amine 10c. Yield 40%. Yellow oil. IR 3425 cm^{-1} (NH). ^{1}H NMR 1.30 (t, 3H, J=7 Hz, CH_3), 3.44–3.54 (m, 2H, CH_2), 4.70 (bs, 1H, NH). ^{13}C NMR 15.0 (CH_3), 37.3 (CH_2), 110.0 (C-4), 145.0 (C-5), 159.0 (C-3). Calcd for $C_5H_6Cl_2N_2S$ (197.09) C 30.47 H 3.07 N 14.21, found C 30.24 H 3.03 N 14.01.

4.5. General procedure for oxidation of 8, 9, 10 to 11, 12, 13

Compounds **8**, **9** or **10** (4.2 mmol) were dissolved in dichloromethane or methanol (50 mL) under stirring and metachloroperbenzoic acid (1.6 g, 9.24 mmol) was added in several portions. The mixture was maintained at 25–40°C until disappearance of the starting material (about 5 h, TLC AcOEt 100%). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (AcOEt/cyclohexane 0:100 to 100:0).

4.5.1. *N*-Benzylisothiazol-3-amine 1,1-dioxide 11a. Yield 80%. Mp 164°C dec. (white powder from Et_2O). IR 3277 cm^{-1}. ^{1}H NMR (CD_3COCD_3) 4.85 (d, 2H, J=4.5 Hz, CH_2), 6.97 (d, 1H, J=5.5 Hz, H_4), 7.36–7.44 (m, 5H, arylH), 7.72 (d, 1H, J=5.5 Hz, H_5), 8.40 (bs, 1H, NH). ^{13}C NMR 46.6 (CH_2), 125.0 (C-4), 127.6, 127.9, 128.5 (arCH), 136.7 (arC), 144.4, (C-5), 161.4 (C-3). Calcd for $C_{10}H_{10}N_2O_2S$ (222.26) C 54.05 H 4.53 N 12.60, found C 53.94 H 4.58 N 12.26.

4.5.2. *N*-Benzyl-5-chloroisothiazol-3-amine 1,1-dioxide 12a. Yield 79%. Mp 118–120°C dec. (white powder from iPr_2O). IR 3313 cm^{-1}. ^{1}H NMR (CD_3COCD_3) 4.72 (d, 2H, J=5.8 Hz, CH_2), 7.05 (s, 1H, H_4), 7.34–7.47 (m, 5H, arylH), 8.60–8.90 (bs, 1H, NH). ^{13}C NMR 45.6 (CH_2), 119.4 (C-4), 127.1, 127.4, 127.9 (arCH), 135.6 (arC), 147.3 (C-5), 159.6 (C-3). Calcd for $C_{10}H_9ClN_2O_2S$ (256.71) C 46.79 H 3.53 N 10.91, found C 46.96 H 3.35 N10.65; *m/z* 256 (M^+), 192, 157.

4.5.3. *N*-Methylisothiazol-3-amine 1,1-dioxide 11b. Yield 66%. Mp 130°C (white powder from Et_2O). IR 3403 cm^{-1}. ^{1}H NMR (CD_3OD) 3.05 (s, 3H, CH_3), 6.85 (d, 1H, J=5.5 Hz, H_4), 7.69 (d, 1H, J=5.5 Hz, H_5). ^{13}C NMR (CD_3COCD_3) 29.3 (CH_3), 125.4 (C-4), 144.7 (C-5), 162.5 (C-3). Calcd for $C_4H_6N_2O_2S$ (146.17) C 32.87 H 4.14 N 19.17, found C 32.56 H 4.16 N19.02.

4.5.4. 5-Chloro-*N*-methylisothiazol-3-amine 1,1-dioxide 12b. Yield 63%. Mp 171°C dec. (white powder from Et_2O). IR 3366 cm^{-1}. ^{1}H NMR 3.18 (d, 3H, J=5.1 Hz, CH_3), 5.95 (bs, 1H, NH), 6.54 (s, 1H, H_4). ^{13}C NMR (CD_3COCD_3) 27.9 (CH_3), 119.2 (C-4), 147.1 (C-5), 160.2 (C-3). Calcd for $C_4H_5ClN_2O_2S$ (180.61) C 26.60 H 2.79 N 15.51, found C 26.78 H 2.54 N 15.23; *m/z* 180 (M^+).

4.5.5. 4,5-Dichloro-*N*-methylisothiazol-3-amine 1,1-dioxide 13b. Yield 56%. Mp 73–76°C (white powder from Et_2O). IR 3344 cm^{-1}. ^{1}H NMR 3.35 (d, 3H, J=5 Hz, CH_3), 6.43 (bs, 1H, NH). ^{13}C NMR 30.3 (CH_3), 124.3 (C-4), 144.0 (C-5), 158.0 (C-3). Calcd for $C_4H_4Cl_2N_2O_2S$ (215.06) C 22.34 H 1.87 N 13.03, found C 22.57 H 1.65 N 12.87; *m/z* 214 ($M^+ - 1$).

4.5.6. *N*-Ethylisothiazol-3-amine 1,1-dioxide 11c. Yield 65%. Mp 97–99°C (white powder from Et_2O). IR 3282 cm^{-1}. ^{1}H NMR 1.32 (t, 3H, J=7.3 Hz, CH_3), 3.51–3.65 (m, 2H, CH_2), 6.69 (bs, 1H, NH), 6.82 (d, 1H, J=5.6 Hz, H_4), 7.41 (d, 1H, J=5.6 Hz, H_5). ^{13}C NMR (CD_3COCD_3) 12.3 (CH_3), 37.1 (CH_2), 124.4 (C-4), 143.4 (C-5), 160.4 (C-3). Calcd for $C_5H_8N_2O_2S$ (160.20) C 37.49 H 5.03 N 17.49, found C 37.38 H 5.02 N 17.48.

4.5.7. 5-Chloro-*N*-ethylisothiazol-3-amine 1,1-dioxide 12c. Yield 62%. Mp 129–132°C (white powder from Et_2O). IR 3297 cm^{-1}. ^{1}H NMR 1.34 (t, 3H, J=7.3 Hz, CH_3), 3.58 (m, 2H, CH_2), 6.71 (s, 1H, H_4), 6.76 (bs, 1H, NH). ^{13}C NMR (CD_3COCD_3) 12.2 (CH_3), 36.9 (CH_2), 119.3

(C-4), 147.1 (C-5), 159.2 (C-3). Calcd for $C_5H_7ClN_2O_2S$ (194.64) C 30.85 H 3.62 N 14.39, found C 30.56 H 3.78 N 14.13.

4.5.8. 4,5-Dichloro-*N*-ethylisothiazol-3-amine 1,1-dioxide 13c. Yield 60%. Mp 189–192°C (white powder from Et_2O). IR 3321 cm^{-1}. ^1H NMR 1.40 (t, 3H, J=7.3 Hz, CH_3), 3.65 (m, 2H, CH_2), 6.25 (bs, 1H, NH). ^{13}C NMR (CD_3OD) 12.5 (CH_3), 38.3 (CH_2), 125.5 (C-4), 142.4 (C-5), 157.1 (C-3). Calcd for $C_5H_6Cl_2N_2O_2S$ (229.08) C 26.21 H 2.64 N 12.23, found C 26.34 H 2.98 N 12.02.

4.5.9. *N*-Cyclohexylisothiazol-3-amine 1,1-dioxide 11d. Yield 74%. Mp 183–186°C (white powder from Et_2O). IR 3282 cm^{-1}. ^1H NMR (CD_3OD)1.27–1.49, 1.65–2.85, 2.02–2.06 (3m, 10H, CH_2), 3.72–3.82 (m, 1H, CH), 6.83 (d, 1H, J=5.6 Hz, H_4), 7.70 (d, 1H, J=5.6 Hz, H_5). ^{13}C NMR (CD_3COCD_3) 24.1, 24.9, 31.5 (CH_2), 52.1 (CH), 125.2 (C-4), 143.8 (C-5), 160.0 (C-3). Calcd for $C_9H_{14}N_2O_2S$ (214.29) C 50.44 H 6.59 N 13.07, found C 50.76 H 6.43 N 12.89; m/z 215 (M^++1).

4.5.10. 5-Chloro-*N*-cyclohexylisothiazol-3-amine 1,1-dioxide 12d. Yield 77%. Mp 155–158°C (white powder from Et_2O). IR 3438 cm^{-1}. ^1H NMR (CD_3OD) 1.27–2.05 (m, 10H, CH_2), 3.79–3.81 (m, 1H, CH), 6.80 (s, 1H, H_4). ^{13}C NMR (CD_3COCD_3) 23.5, 24.3, 30.8 (CH_2), 51.4 (CH), 119.4 (C-4), 146.9 (C-5), 158.3 (C-3). Calcd for $C_9H_{13}ClN_2O_2S$ (248.73) C 43.46 H 5.27 N 11.26, found C 43.35 H 5.18 N 11.09.

4.5.11. *N*-Phenylisothiazol-3-amine 1,1-dioxide 11e. Yield 82%. Mp 174–176°C dec. (Et_2O). IR 3226 cm^{-1}. ^1H NMR (DMSO-d_6) 7.11 (d, 1H, J=5.7 Hz, H_4), 7.24–7.79 (m, 5H, arylH), 8.15 (d, 1H, J=5.7 Hz, H_5). ^{13}C NMR (CD_3OD) 121.1 (C-4), 125.9, 126.9, 129.2 (arCH), 137.9 (arC), 142.6 (C-5), 158.5 (C-3). Calcd for $C_9H_8N_2O_2S$ (208.24) C 51.91 H 3.87 N 13.45, found C 51.74 H 3.98 N 13.23; m/z 208 (M^+).

4.5.12. 5-Chloro-*N*-phenylisothiazol-3-amine 1,1-dioxide 12e. Yield 35%. Mp 200°C dec. (white powder from Et_2O). IR 3292 (NH) cm^{-1}. ^1H NMR (CD_3COCD_3) 7.19 (s, 1H, H_4), 7.20–7.40, 7.40–7.60, 7.80–7.90 (3m, 5H, arylH), 10.30–10.50 (bs, 1H, NH). ^{13}C NMR (CD_3COCD_3) 121.4, 121.5, 126.2, 129.5 (C-4+arCH), 137.5 (arC), 147.3 (C-5), 157.5 (C-3). Calcd for $C_9H_7ClN_2O_2S$ (242.68) C 44.54 H 2.91 N 11.54, found C 44.76 H 2.98 N 11.20.

4.5.13. *N*-(4-Methylbenzyl)isothiazol-3-amine 1,1-dioxide 11f. Yield 50%. Mp 159–162°C (white powder from Et_2O). IR 3092 cm^{-1}. ^1H NMR (CD_3OD) 2.25 (s, 3H, CH_3), 4.68 (CH_2), 6.85 (d, 1H, J=5.8 Hz, H_4), 7.24 (d, 2H, J=8 Hz, arylH), 7.27 (d, 2H, J=8 Hz, arylH), 7.72 (d, 1H, J=5.8 Hz, H_5). ^{13}C NMR (CD_3OD) 19.9 (CH_3), 46.7 (CH_2), 125.7 (C-4), 128.1, 129.3 (arCH), 133.4, 137.8 (arC), 143.8 (C-5), 161.8 (C-3). Calcd for $C_{11}H_{12}N_2O_2S$ (236.29) C 55.91 H 5.12 N 11.86, found C 55.75 H 5.18 N 11.73; m/z 236 (M^+).

4.5.14. 5-Chloro-*N*-(4-methylbenzyl)isothiazol-3-amine 1,1-dioxide 12f. Yield 65%. Mp 148–150°C (white powder from Et_2O). IR 3200 (NH) cm^{-1}. ^1H NMR 2.40 (s, 3H, CH_3), 4.60 (CH_2), 6.45–6.60 (bs, 1H, NH), 6.56 (s, 1H, H_4), 7.18 (d, 2H, J=8.4 Hz, arylH), 7.24 (d, 2H, J=8.4 Hz, arylH), 7.72 (d, 1H, J=5.8, H_5). ^{13}C NMR 22.0 (CH_3), 46.0 (CH_2), 122.0 (C-4), 128.0, 130.0 (arCH), 134.0, 138.0, 146.0 (arC, C-5), 160.0 (C-3). Calcd for $C_{11}H_{11}ClN_2O_2S$ (270.74) C 48.80 H 4.10 N 10.35, found C 48.95 H 3.95 N 10.01.

4.5.15. 5-Chloro-*N*-(4-nitrobenzyl)isothiazol-3-amine 1,1-dioxide 12h. Yield 70%. Mp 218°C dec. (white powder from Et_2O). IR 3266 cm^{-1}. ^1H NMR (CD_3COCD_3) 4.92 (s, 2H, CH_2), 7.12 (s, 1H, H_4), 7.75 (d, 2H, AB syst., J=8.8 Hz, arylH), 8.28 (d, 2H, AB syst., J=8.8 Hz, arylH), 8.99 (bs, 1H, NH). ^{13}C NMR 45.8 (CH_2), 123.3, 129.2 (arCH), 120.4 (C-4), 144.4, 147.0, 148.0 (arC, C-5), 161.1 (C-3). Calcd for $C_{10}H_8ClN_3O_4S$ (301.71) C 39.81 H 2.67 N 13.93, found C 39.56 H 2.90 N 13.90.

4.5.16. Ethyl [(1,1-dioxidoisothiazol-3-yl)amino]acetate 11i. Yield 56%. Yellow oil. IR 3300 (NH), 1730 (CO) cm^{-1}. ^1H NMR (CD_3COCD_3) 1.28 (t, 3H, J=7 Hz, CH_3), 4.25 (q, 2H, J=7 Hz, CH_2), 4.29–4.33 (m, 2H, CH_2), 7.13 (d, 1H, J=5.5 Hz, H_4), 7.75 (d, 1H, J=5.5 Hz, H_5), 8.30–8.40 (bs, 1H, NH). ^{13}C NMR (CD_3COCD_3) 13.7 (CH_3), 44.4 (CH_2), 61.4 (OCH_2), 125.1 (C-4), 145.0 (C-5), 162.2 (C-3), 168.3 (CO). Calcd for $C_7H_{10}N_2O_4S$ (218.23) C 38.53 H 4.62 N 12.84, found C 38.76 H 4.60 N 12.76.

4.5.17. Methyl 2-[(1,1-dioxidoisothiazol-3-yl)amino]-3-phenylpropanoate 11l. Yield 78%. Mp 153–154°C (white powder from Et_2O). IR 3300 (NH), 1745 (CO) cm^{-1}. ^1H NMR 3.27–3.49 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 5.02 (m, 1H, CH), 6.21 (bs, 1H, NH), 6.63 (d, 1H, J=5.5 Hz, H_4), 7.04–7.32 (m, 5H, arylH), 7.49 (d, 1H, J=5.5 Hz, H_5). ^{13}C NMR 37.2 (CH_2), 53.2, 57.1 (CH_3+CH), 125.2, 127.8, 129.1, 129.5 (arCH+C-4), 134.9 (arC), 144.5 (C-5), 161.0 (C-3), 171.3 (CO). Calcd for $C_{13}H_{14}N_2O_4S$ (294.33) C 53.05 H 4.79 N 9.52, found C 53.16 H 4.56 N 9.45; m/z 294 (M^+).

4.5.18. *N*-Benzyl-4-bromoisothiazol-3-amine 1,1-dioxide 15. Compound **11a** (500 mg, 2.25 mmol) was dissolved in a mixture of CH_2Cl_2 (25 mL) and CCl_4 (5 mL) under stirring and Br_2 (356 mg, 2.25 mmol) in 3 mL di CCl_4 was slowly dropped into the solution. The reaction was checked by TLC until disappearance of the starting material (15 h, cyclohexane/AcOEt 6:4). At the end of the reaction, TEA (227 mg, 2.25 mmol) was added and stirring was continued for additional 15 h. The reaction was quenched with diluted HCl (10% solution, 10 mL) and transferred to a separatory funnel and the organic layer separated. This last was washed twice with water (10 mL) and then with a saturated solution of $Na_2S_2O_5$. The organic layer was separated, dried with Na_2SO_4 and the solvent evaporated at reduced pressure. The residue was chromatographed on silica gel (eluent: cyclohexane/AcOEt 100:0 to 0:100) and **15** crystallized with Et_2O. Yield 77%. Mp 185–187°C (white powder from Et_2O). IR 3313 cm^{-1} (NH). ^1H NMR (CD_3COCD_3) 4.74 (d, 2H, CH_2; J=6.2 Hz), 7.32–7.47 (m, 5H, arylH), 8.19 (s, 1H, H-5), 8.56 (bs, 1H, NH). ^{13}C NMR (CD_3COCD_3) 47.63 (CH_2), 119.73 (C-4), 128.11, 128.49, 128.95 (arCH), 137.17 (arC), 143.79 (C-5), 15.51 δ (C-3). Calcd for $C_{10}H_9BrN_2O_2S$ (301.16) C 39.88, H 3.01, N 9.30, S 10.65, found C 39.66 H 2.89, N 9.35, S 10.62

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