Isothiazolo[5,4-*d*]isoxazole *S,S*-dioxides and Pyrazolo [3,4-*d*]-isothiazole *S,S*-dioxides through Cycloaddition Reaction on 3-Benzylaminoisothiazole *S,S*-dioxides

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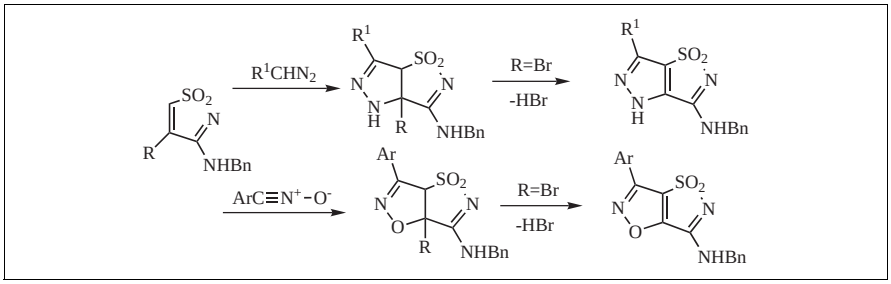

By reacting 4,5-unsubstituted isothiazole dioxides with diazoalkanes and nitrile oxides bicyclic pyrazolo[3,4-*d*]isothiazole and isothiazolo[5,4-*d*]isoxazole *S,S*-dioxides were obtained in good yield through a regioselective cycloaddition reaction. Through cycloaddition reaction of 3-benzylamino-4-bromo-isothiazole *S,S*-dioxide labile cycloadducts were formed that underwent *in situ* dehydrobromination affording the corresponding aromatized compounds.

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Introduction.

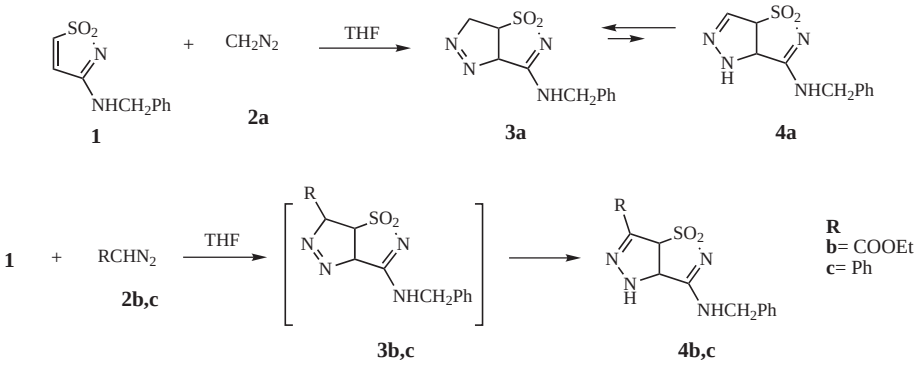
For some years we have been interested in the reactivity of 3-amino-isothiazole dioxide [1-3]. Recently we described a simple method allowing the preparation of isothiazole dioxides unsubstituted at C-4 and C-5 and of the related mono- and di-halogeno derivatives carrying on C-3 a secondary amino group [4]. These compounds appeared to be very attractive as the key starting material for the synthesis of a large number of isothiazole dioxide derivatives. It has to be remembered that several representatives of the 3-aminoisothiazole dioxide series display an interesting biological activity as antiproliferating agents presumably through inhibition of protein prenylation [5,6]. In continuing our research on this nucleous we planned a study aiming to obtain bicyclic system where the isothiazole dioxide moiety would be condensed with different heterocyclic nuclei. Taking advantage of the C-4 C-5 double bond, the bicyclic system could in principle be derived from a 1,3-dipolar cycloaddition reaction with several dipoles. In this paper we describe the reactivity of 3-benzylamino-isothiazole dioxide and of mono- and dihalogeno-3-benzylamino-isothiazole dioxides with 1,3-dipoles aiming to synthesize various bicyclic systems able to undergo useful ring transformation reactions. Furthermore, the constraining resulting in these systems could have important consequences in the interaction of the isothiazole moiety with the bioreceptorial site.

Results and Discussion.

3-Benzylamino-isothiazole dioxide **1** was reacted with several diazoalkanes and nitrile oxides as the dipoles. By reacting **1** with an ethereal solution of diazomethane (**2a**), **3a** as the sole reaction product was obtained in a very good yield (90%). The pyrazoline **3a** is stable in the reaction conditions and doesn't isomerize to the corresponding Δ_2-pyrazoline **4a**. When the same reaction was performed with **2b,c** compounds **4b,c** were obtained through tautomerization of the primary cycloaddition product, the Δ_1-pyrazoline **3b,c**. The greater thermodynamic stability of 2-pyrazolines with respect to the corresponding 1-tautomers is well documented and is enhanced by substituents on C-3 which can contribute to the stabilization of the C=N bond [7]. In line with this expectation only 2-pyrazolines were obtained directly from the reactions of **1** with phenyldiazomethane and ethyl diazoacetate. The structures of the bicyclic compounds **3a** and **4b,c** were confirmed by analytical and spectroscopic data and the regiochemistry was established by performing NOESY experiments. The activation of the double bond is strong enough to render its cycloaddition reaction possible in very mild conditions. Moreover, it has to be underlined that the reaction is completely regioselective, affording only one regioisomer. The regiochemistry is the same showed by 3-dialkylamino-isothiazole dioxides bearing an aryl substituent on C-4

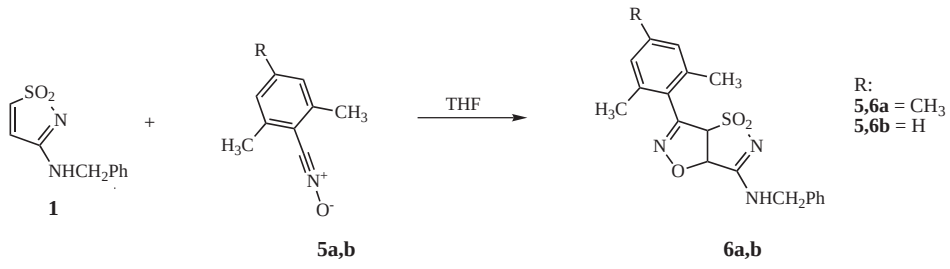
when reacted with the same dipoles in 1,3-dipolar cycloadditon reactions [8]. In principle, the lack of the aromatic ring at C-4 in compound **1** could influence substantially the reactivity of the system both altering the electronic distribution on the C-4-C-5 double bond and strongly reducing the steric hindrance. Notwithstanding, it is evident that the absence of the substituent on C-4 is of negligible consequence in directing the reaction.

Scheme 1



Compound **1** was reacted also with nitrile oxides **5a,b** affording **6a,b** as the sole reaction product in satisfactory yield confirming the good reactivity of **1** as dipolarophile in 1,3-dipolar cycloaddition reaction. The structure of **6** was assigned by virtue of analytical and spectroscopic data and the regiochemistry was established by performing NOESY experiments. Also in this case, **1** underwent smooth reaction with the dipolarophiles to give rise to the corresponding cycloadduct in a complete regioselective manner [9,10].

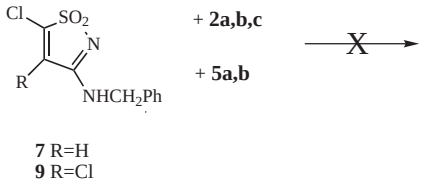
Scheme 2



Aiming to obtain the corresponding aromatic systems, we tried to dehydrogenate the bicyclic compounds **3a**, **4b,c**, **6a,b**. Any attempt (NiO_2, MnO_2, DDQ) was unsuccessful affording only tars or recovering the unreacted reagents. To overcome this problem, we thought to take advantage of the reactivity as dipolarophile of the 5-chloroisothiazole dioxide **7** and/or the 4-bromo-isothiazole dioxide **8** to carry out the cycloaddition reaction followed by *in situ* dehydrohalogenation.

Compound **7** gave unsatisfactory results even with diazoalkanes or with nitrile oxides. Operating with equimolecular amount of dipoles and at room temperature only unreacted **7** was recovered. Operating with excess of dipoles and/or at the refluxing temperature of several solvents (dichloromethane, benzene, toluene, xilene) compound **7** disappeared from the reaction but only degradation products was observed. Only in the case of **5a**, by using THF at reflux, traces of the cycloaddition product were shown by ^{1}H NMR analysis of the crude reaction mixture together with degradation products. During these experiments also compound **9** was tested as dipolarophile with the same dipoles but gave unsatisfactory results as for **7**.

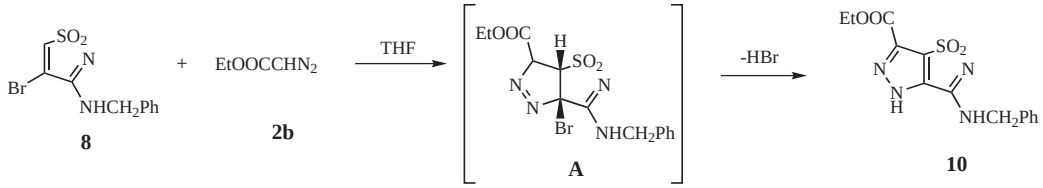
Scheme 3



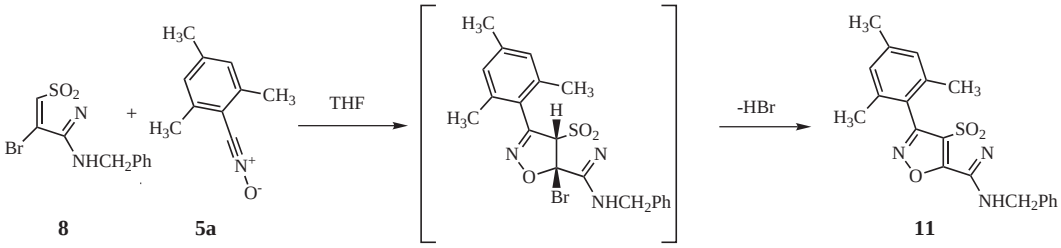
On the contrary, compound **8** reacted satisfactory with diazoalkane **2b** affording, directly, compound **10** as the sole reaction product. The confirmation of the assigned

structure derived from NMR considerations together with analytical data. The ^{1}H NMR spectra show the signals associated with the benzylamino group and those characteristic of the pyrazoline derived from the cycloaddition but the signal associable with H-*3a* in A is absent. Moreover, in the ^{13} C NMR any CH signals are absent except for those associable to the phenyl rings and two quaternary carbon atoms associable with C-*3a* and C-*6a* in **10** are present. The primary cycloaddition product A is evidently labile and spontaneously aromatize to **10**. The same outcome was observed by reacting **8** with **5a**, where only **11** through *in situ* dehydrohalogenation being observed.

Scheme 4



Scheme 5



Conclusions.

These results demonstrated the good reactivity of **1** as dipolarophile in 1,3-dipolar cycloaddition reaction with diazoalkanes and nitrile oxides. Moreover this cycloaddition showed a very high grade of selectivity only one regioisomer in each reaction being obtained. The regiochemistry of the cycloaddition is the same showed by the already known 3-amino-4-arylisothiazole dioxides so that the lack of the aryl substituent is apparently of little consequence in directing the reaction. The 4-bromoderivative **8** is also a good dipolarophile and reacted efficiently affording labile cycloadducts that dehydrobrominated spontaneously to the aromatic bicylic systems **10** and **11**. Also this dipolarophile gave rise to a completely regioselective reaction. By this very simple, mild and efficient pathway, a strategy to produce bicyclic systems with nitrogen heterocycles (*i.e.* pyrazoline or isoxazoline) condensed with the isothiazole dioxide moiety was developed. Biological studies are in progress in order to evaluate if constrained substituents could change the activity of the isothiazole nucleous as inhibitor of cell proliferation.

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. 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 Finnigan INCOS 50 or from a Finnigan MD 800 instruments using the direct exposure probe (DEP). Compounds **1,7,8,9** have already been described [3].

N-Benzyl-6,6a-dihydro-3a*H*-pyrazolo[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**3a**).

Compound **1** (0.4 g, 1.8 mmol) was dissolved in THF gently heating (40-50 °C). The solution was then allowed to return to room temperature and an ethereal solution of CH_2N_2 was added. Stirring was continued until disappearance of the starting material (best check with ^{1}H-NMR, about 72 h). Solvent was evaporated under reduced pressure and **3a** crystallized from diethyl ether. Yield 90%. M.p. 121 °C (white powder). IR (nujol) 3290 cm^{-1}(NH); ^{1}H-NMR (CD_3COCD_3): δ 3.98 (dt, 1H, *J* 2.2, 8.4, H_{6a}); 4.68 (d, 2H, *J* 5.5, CH_2Ph); 5.00 (ddd, 1H, *J* 8.4, 19.0, 1.8, $H_{6'}$); 5.36 (dt, 1H, *J* 2.2, 2.5, 19.0, H_6); 6.44 (dt, 1H, *J* 8.4, 2.5, 1.8, H_{3a}); 7.32-7.47 (m, 5H, aryl-H); 8.94 (bs, 1H, NH); ^{13}C-NMR 46.36; 52.65; 80.42; 97.92; 126.80; 127.09; 127.77; 136.34; 160.40.

Anal. Calcd. for $C_{11}H_{12}N_4O_2S$ (264.30) C, 49.99; H, 4.58; N, 21.20; Found C, 49.68; H, 4.67; N, 21.10.

Ethyl 3-benzylamino-6,6a-dihydro-3a*H*-pyrazolo[3,4-*d*]isothiazol-6-carboxylate 1,1-dioxide (**4b**).

Compound **1** (0.52 g, 2.36 mmol) was dissolved in THF gently heating (40-50°C). The solution was then allowed to

return to room temperature and ethyl diazoacetate **2b** (0.269 g, 2.36 mmol) was added. The mixture was refluxed under stirring until disappearance of the starting material (TLC acOEt/cyclohexane 4:1, about 20 h). Solvent was evaporated under reduced pressure and **4b** crystallized from diethyl ether. Yield 90%. M.p. 130°C dec. (white powder). IR (nujol) 3334 cm^{-1}(NH); ^{1}H-NMR (CD_3COCD_3): δ 1.32 (t, 3H, *J* 7.0, CH_3); 4.28 (q, 2H, *J* 7, CH_2); 4.62 (d, 2H, *J* 5.5, CH_2Ph); 5.07 (d, 1H, *J* 11.4, H_{6a}); 5.86 (dd, 1H, *J* 11.4, 2.6, H_{3a}); 7.30-7.42 (m, 5H, aryl-H); 8.27 (bs, 1H, NH); 8.49 (bs, 1H, H_4); ^{13}C-NMR 12.85; 46.34; 59.66; 66.54; 69.99; 126.82; 127.13; 127.79; 134.57; 136.20; 157.7; 163.32.

Anal. Calcd. for $C_{14}H_{16}N_4O_4S$ (336.37) C, 49.99; H, 4.79; N, 16.66; Found C, 50.12; H, 4.55; N, 16.54.

N-Benzyl-6-phenyl-6,6a-dihydro-3a*H*-pyrazolo[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**4c)**.

Compound **1** (0.1 g, 0.45 mmol) was dissolved in THF gently heating (40-50 °C). The solution was then brought to 10 °C and an ethereal solution of phenyldiazomethane **2c** freshly prepared was added. The mixture was stirred until disappearance of the starting material (TLC acOEt/cyclohexane 1:1, about 2 h). Solvent was evaporated under reduced pressure without heating and **4c** crystallized from diethyl ether. Yield 90%. M.p. 157 °C dec. (white powder). IR (nujol) 3320 cm^{-1}(NH); ^{1}H-NMR (DMSO): δ 4.50 (d, 2H, *J* 4.8, CH_2Ph); 5.40 (d, 1H, *J* 11.0, H_{6a}); 5.50 (dd, 1H, *J* 11.0, 4.4, H_{3a}); 7.32-7.69 (m, 5H, aryl-H); 7.98 (d, 1H, *J* 4.4, H_4); 9.26 (bs, 1H, NH); ^{13}C-NMR 47.25; 65.51; 71.24; 126.43; 128.18; 128.45; 129.27; 129.37; 130.05; 132.32; 137.83; 144.83; 166.06.

*Anal.*Calcd. for $C_{17}H_{16}N_4O_2S$ (340.40) C, 59.98; H, 4.74; N, 16.46; Found C, 59.66; H, 4.60; N, 16.25.

N-Benzyl-3-(2,4,6-trimethylphenyl)-3a,6a-dihydroisothiazolo-[5,4-*d*]isoxazol-6-amine 4,4-dioxide (**6a**).

Compound **1** (0.05 g, 0.225 mmol) was dissolved in THF gently heating (40-50 °C). The solution was then allowed to return to room temperature and **5a** (76 mg, 0.472 mmol) was added. The mixture was stirred until disappearance of the starting material (TLC acOEt/cyclohexane 3:2, about 20 h). Solvent was evaporated under reduced pressure and the residue chromatographed on silica gel (acOEt/cyclohexane 0:100 to 100:0). **6a** crystallized from diethyl ether. Yield 85%. M.p. 197 °C. (white powder). IR (nujol) 3290 cm^{-1}(NH); ^{1}H-NMR: δ 2.29 (s, 9H, CH_3); 4.64 (m, 2H, CH_2); 5.33 (d, 1H, *J* 9.1, H_{3a}); 5.96 (d, 1H, *J* 9.1, H_{6a}); 6.19 (bs, 1H, NH); 6.94 (s, 2H, Me_3ArH); 7.28-7.44 (m, 5H, aryl-H); ^{13}C-NMR (CD_3COCD_3): δ 20.29; 20.58; 47.41; 71.97; 85.67; 123.90; 128.05; 128.21; 128.98; 129.28; 137.32; 137.91; 139.57; 152.90; 164.42.

Anal. Calcd. for $C_{20}H_{21}N_3O_3S$ (383.13) C, 62.64; H, 5.52; N, 10.96; Found C, 62.40; H, 5.62; N, 10.75.

N-Benzyl-3-(2,6-dimethylphenyl)-3a,6a-dihydroisothiazolo[5,4-*d*]isoxazol-6-amine 4,4-dioxide (**6b**).

Compound **1** (0.1 g, 0.45 mmol) was dissolved in THF gently heating (40-50 °C). The solution was then allowed to return to room temperature and **5b** (66 mg, 0.45 mmol) was added. The mixture was stirred until disappearance of the starting material (TLC acOEt/cyclohexane 3:2, about 48 h). Solvent was evaporated under reduced pressure and the residue crystallized from diethyl ether affording **6b**. Yield 90%. M.p. 230-232 °C. (white powder). IR (nujol) 3324 cm^{-1}(NH); ^{1}H-NMR (CD_3COCD_3): δ 2.37 (s, 6H, CH_3); 4.70 (m, 2H, CH_2); 5.60 (d, 1H, *J* 9.2, H_{3a}); 6.43 (d, 1H, *J* 9.2, H_{6a}); 7.12-7.43 (m, 8H, aryl-H); 8.66 (bs, 1H, NH); ^{13}C-NMR 19.11; 46.28; 70.77; 84.48; 125.70; 126.86; 127.04; 127.29; 128.61; 136.14; 136.92; 151.70; 163.32.

Anal. Calcd. for $C_{19}H_{19}N_3O_3S$ (369.44) C, 61.77; H, 5.18; N, 11.37; Found C, 61.90; H, 5.02; N, 11.12.

Ethyl 3-benzylamino-4*H*-pyrazolo[3,4-*d*]isothiazole 6-carboxylate (**10**).

Compound **8** (0.226 g, 0.75 mmol) was dissolved in THF and ethyl diazoacetate **2b** (0.86 g, 0.75 mmol) was added. The mixture was refluxed under stirring until disappearance of the starting material (TLC acOEt/cyclohexane 4:1, about 48 h). Solvent was evaporated under reduced pressure and the residue oil crystallized from CH_2Cl_2/diethyl ether. Yield 74%. M.p. 122-124 °C. (white powder). IR (nujol) 1722 (CO), 3319, 3537 cm^{-1} (NH); ^{1}H-NMR: δ 1.43 (t, 3H, *J* 7.0, CH_3); 4.43 (q, 2H, *J* 7.0, CH_2); 4.73 (d, 2H, *J* 5.6); 6.82 (bs, 1H, NH); 7.39 (2, 5H, aryl-H); 11.9-12.5 (bs, 1H, NH); ^{13}C-NMR 14.03; 47.79; 63.89; 128.24; 128.83; 128.89; 129.40; 136.10; 151.94; 154.03; 157.66; 162.45.

Anal. Calcd. for $C_{15}H_{16}N_4O_4S$ (348.38) C, 51.70; H, 4.63; N, 16.08. Found C, 51.87; H, 4.85; N, 15.90.

N-Benzyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[5,4-*d*]isoxazol-6-amine 4,4-dioxide (**11**).

Compound **9** (0.174 g, 0.49 mmol) was dissolved in THF (5 mL) and nitrile oxide **5a** (0.78 g, 0.49 mmol) was added. The mixture was refluxed under stirring until disappearance of the starting material (TLC acOEt/cyclohexane 4:1, about 48 h). Solvent was evaporated under reduced pressure the residue cromatographed on silica gel (acOEt/cyclohexane 0:100 to 100:0). **11** crystallized from CH_2Cl_2/diisopropyl ether. Yield 87%. M.p. 103-105 °C. (white powder). IR (nujol) 3267 cm^{-1} (NH); ^{1}H-NMR: δ 2.24 (s, 6H, CH_3); 2.31 (s, 3H, CH_3); 4.71 (d, 2H, *J* 5.86); 6.54 (bs, 1H, NH); 6.94 (m, 2H, aryl-H);7.40 (m, 5H, aryl-H); ^{13}C-NMR: δ 22.23; 22.62; 50.14; 129.62; 134.88; 135.00; 135.24; 146.39; 147.90; 148.84; 150.12; 155.21; 168.35; 178.02.

Anal. Calcd. for $C_{20}H_{19}N_3O_3S$ (381.45) C, 62.97; H, 5.02; N, 11.02. Found C, 63.13; H, 5.06; N, 10.78.

REFERENCES

[1] F. Clerici, L. Lo Presti, M. L. Gelmi, R. Soave, *Tetrahedron* **58**, 5173 (2002).

[2] F. Clerici, M. L. Gelmi, E. Pini, M. Valle, *Tetrahedron* **57**, 5455 (2001).

[3] F. Clerici, "Thiazole and Thiadiazole S-oxides" Advances in Heterocyclic Chemistry, A. R. Katritzky ed., Pergamon Press, **83**, 72, (2002).

[4] F. Clerici, A. Contini, M. L. Gelmi, D. Pocar, *Tetrahedron* **59**, 9399 (2003)

[5] F. Clerici, M. L. Gelmi, K. Yokoyama, D. Pocar, W. C. Van Voorhis, F. S. Buckner, M. H. Gelb, *Bioorg. Med. Chem. Lett.*, **12**, 2217 (2002).

[6] N. Ferri, F. Clerici, K. Yokoyama, D. Pocar, A. Corsini, *Biochemical Pharmacology* **70**, 1735 (2005).

[7] J. Elguero, in Comprehensive Heterocyclic Chemistry, eds. A. Katritzky and T. Potts, Pergamon Press, Oxford, 1984, vol. **5**, pp.167-302.

[8] F. Clerici, T. Ferrario, M. L. Gelmi, R. Marelli, *J. Chem. Soc. Perkin Trans. I*, 2533 (1994).

[9] H. Zhang, W. H. Chan, Albert W. M. Lee, W. Y. Wong, P. F. Xia, *Tetrahedron: Asymmetry* **16**, 761, (2005).

[10] H. Zhang, W. H. Chan, Albert W. M. Lee, W. Y. Wong, *Tetrahedron Letters* **44**, 395, (2003).