1,3-Dipolar Cycloaddition Reactions of Isothiazol-3(2*H*)-ones with Nitrile Oxides. An Unexpected Site Selectivity of the Carbonyl Bond of 5-Benzoyl-isothiazol-3(2*H*)-one

E. Coutouli-Argyropoulou* and C. Anastasopoulos

Laboratory of Organic Chemistry, University of Thessaloniki, Thessaloniki, GR 540 06, Greece

February 27, 1996

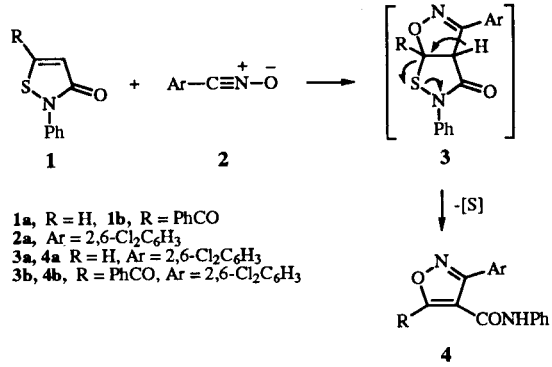
Dedicated to the memory of Professor Nicholas Alexandrou

2,6-Dichlorobenzonitrile oxide (**2a**) reacts with isothiazolones **1a** and **1b** at the ethylenic double bond to give **4** *via* transformation of the primary cycloadducts **3**. Mesitonitrile oxide (**2b**) adds preferentially to the carbonyl double bond of **1b** yielding the monoadduct **5** and the bisadduct **6**.

J. Heterocyclic Chem., **33**, 731 (1996).

Isothiazol-3(2*H*)-ones consist of an interesting class of heterocyclic compounds with many biological and industrial applications [1]. One of the most known synthetic isothiazolone derivatives is the benzothiazol-3(2*H*)-one 1,1-dioxide, better known as saccharin. 1,3-Dipolar-cycloaddition and Diels-Alder reactions to isothiazol-3(2*H*)-one 1,1-dioxides have to be proven good processes for the synthesis of several saccharin derivatives, which further are converted to oxicams, a widely used class of anti-inflammatory agents [2-5]. Isothiazol-3(2*H*)-one 1-oxides are also reactive dienophiles and give Diels-Alder cycloaddition reactions under mild conditions [6,7]. By contrast the unoxidized isothiazol-3(2*H*)-ones are referred as poor dienophiles, which were found not to react with several of the more reactive dienes [6]. For reasons of comparison and in connection with our interest in the construction of novel multi-ring heterocycles *via* 1,3-dipolar cycloaddition reactions [8-10], we investigated the 1,3-dipolar cycloaddition reactions of isothiazol-3(2*H*)-ones with stable nitrile oxides.

Reactions of isothiazolones **1a** and **1b** with the stable nitrile oxides **2a** and **2d** were carried out by reflux of a methylene chloride or chloroform solution of the reactants for 10-30 hours using nitrile oxide in excess (1.5:1). 2,6-Dichloronitrile oxide (**1a**) reacted with both **2a** and **2b** to give the cycloaddition products to the carbon-carbon double bond **3**. Compounds **3** were not isolated, but by working up the reaction mixture with column chromatography they were transformed to the isoxazoles **4a** and **4b**, which were isolated in 45 and 55% yield respectively. The formation of the fused isoxazolines **3** was detected from the ^{1}H nmr of their reaction mixtures. Thus the ^{1}H nmr or the reaction mixture of **1a** with **2a** shows two doublets at δ 7.02 and 5.09 corresponding to 6a-H and 3a-H of the fused isoxazoline **3a** and that of the reaction of **1b** with **2a** shows one singlet at δ 5.98 corresponding to the 3a-H of the fused isoxazoline **3b**. The spectral data of the isolated isoxazoles **4a** and **4b** are in accordance with the proposed structures. Especially the ^{1}H nmr of **4a** shows a down field singlet at δ 9.16, characteristic of an hydrogen at the 5-position of the isoxazole ring [11], thus supporting the



1 **2** **3**

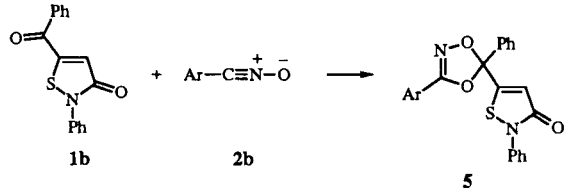
1a, R = H, **1b**, R = PhCO
2a, Ar = 2,6-$Cl_2C_6H_3$
3a, **4a** R = H, Ar = 2,6-$Cl_2C_6H_3$
3b, **4b**, R = PhCO, Ar = 2,6-$Cl_2C_6H_3$

4

proposed structure of the 4-substituted isoxazole instead of the other possible regioisomeric structure of 5-substituted isoxazole. The proton chemical shifts of the intermediate isoxazolines are also consistent with structure **3**, in which the down field chemical shift of 6a-H is the result of the two electronegative substituents (oxygen and sulfur) attached to the C-6a. The proposed regiochemistry of the addition is in agreement with that observed with other enonic systems, containing in conjugation electron donor substituents [12,13]. In all cases the electron donor substituent controls the regiochemistry of the reactions leading to 4-carboxy-derivatives. Thus the sulfur atom of the isothiazolone ring seems to be the pivotal regiocontrolling factor of the cycloadditions studied. By contrast, the opposite regioselectivity has been observed in the cycloadditions to isothiazol-3(2*H*)-one 1,1-dioxides [2]. In this case the sulfonyl group is ignored for the purpose of predicting regioselectivity. The transformation of **3** to the isoxazoles **4** by loss of sulfur is probably derived by the tendency of isoxazoline ring for aromatization and the susceptibility of S-N bond to cleavage. A similar sulfur dioxide elimination is also observed in the cycloadducts of thiazol-3(2*H*)-one 1,1-dioxides.

Mesitonitrile oxide **2b** shows a quite different behavior towards isothiazolones **1a** and **1b**. Thus isothiazolone **1a** failed to give any cycloaddition product under several reaction conditions employed. Isothiazolone **1b** was more reactive and gave the mono and bis cycloadducts **5** and **6** in 50

and 15% yield respectively. Compound **5** is the cycloaddition product to the carbonyl bond of the benzoyl group from its spectral data. In the mass spectrum it gives molecular ion and fragments of retro cycloaddition; in the ^{1}H nmr there is the chemical shift of ethylenic hydrogen at δ 6.38, whereas in the ^{13}C nmr the benzoyl carbonyl chemical shift, which in **1b** appears at δ 187, is missing. The bis-cycloadduct **6** was isolated as a mixture of two diastereoisomers in a ratio 1.5:1, as it comes out from the chemical shifts of isoxazoline ring protons at δ 4.91 and 4.95. Its spectral data are in agreement with the proposed structure of a double cycloaddition product to the benzoyl carbonyl bond and to the ethylenic bond of the thiazolone ring. In the mass spectrum it gives fragments of retro dipolar cycloaddition whereas in the ^{13}C nmr the benzoyl carbonyl chemical shift is also missing. The mentioned isoxazoline proton chemical shifts as well as the C-3a and C-6a carbon chemical shifts at δ 65.2, 65.1 and 102.3, 102.1 respectively support the proposed regiochemistry for the cycloaddition to the ethylenic double bond. In the opposite regioisomer the isoxazoline proton chemical shift should be at a higher frequency and the difference in the carbon chemical shifts should be much smaller. Concerning the relative stability of bisadduct **6** compared with that of **3**, it can be attributed to the sterically decreased mobility of the 3a-H atom in the condensed isoxazoline **6**. Thus **6** is isolated from column chromatography, whereas **3** is transformed to **4**.



The observed site selectivity in the reaction of **1b** with **2b** is rather unexpected since carbonyl bonds usually show low reactivity towards cycloaddition with nitrile oxides [14]. Only activated carbonyls with electron-withdrawing groups or strained carbonyls belonging to cyclic systems are known to react readily and in a few cases predominantly with nitrile oxides [15,16]. On the basis of FMO calculations, it is accepted that cycloadditions of nitrile oxides with carbon-carbon double bonds are mainly HOMO-dipole controlled, whereas those to carbon-oxygen double bonds are LUMO-dipole controlled [16]. Thus mesitonitrile oxide **1b** having a higher HOMO reacts more readily with carbonyl bonds. In the case of **1b** it is the isothiazolone ring which acts as an electron withdrawing group [1], activates the carbonyl and makes it more reactive towards mesitonitrile oxide, whereas dichlorobenzonitrile oxide **1a** having a lower LUMO adds preferentially to the carbon-carbon double bond.

In conclusion unoxidized isothiazol-3(2*H*)-ones show moderate dipolarophilicity towards nitrile oxides and the unsubstituted **2a** gives cycloaddition product only with the more reactive dichlorobenzonitrile oxide. On the other hand the isothiazolone ring as an electron-withdrawing group activates carbonyl substituents for cycloaddition.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The ir spectra were taken with a Perkin-Elmer 297 spectrometer. The ^{13}C nmr spectra were recorded with a Bruker AM-300 spectrometer and the ^{1}H nmr spectra with either Bruker AW-300 or AW-80 spectrometers in deuteriochloroform with tetramethysilane as internal standard. The mass spectra were measured with a Hitachi Perkin Elmer RMU-6L spectrometer with an ionization energy or 70eV. Elemental analyses were performed with a Perkin-Elmer analyser Model 240B. Column chromatography was carried out on Merck Kieselgel 60 (particle size 0.063-0.200 mm).

Preparation of Starting Materials.

5-Benzoyl-isothiazol-3(2*H*)-one (**1b**) was prepared by reaction of N-phenyl-3-benzoylpropionamide and thionyl chloride according to a known procedure [17]. Isothiazol-3(2*H*)-one (**1a**) was obtained by debenzoylation of **1b** with sodium hydroxide [18]. 2,6-Dichlorobenzonitrile oxide (**2a**) and mesitonitrile oxide (**2b**) were prepared according to known procedures by reaction of the corresponding aldoximes with *N*-bromosuccinimide and triethylamine [19]. The melting points and the spectral data (ir, ^{1}H nmr) of compounds **1a**, **1b** are in accordance with those reported in the literature [17,20]. In the ^{13}C nmr the following chemical shifts are reported; compound **1a**, ^{13}C nmr: δ 167.5, 139.7, 136.4, 129.2, 127.3, 124.6, 114.7; compound **1b**, ^{13}C nmr: δ 187.0, 166.6, 153.6, 136.1, 135.1, 134.2, 129.4, 129.2, 128.9, 127.9, 124.6, 120.6.

Reaction of Thiazolone **1a** with Nitrile Oxide **2a**.

A solution of **1a** 0.187 g (1 mmole) and nitrile oxide **2a** 0.282 g (1.5 mmoles) in dry methylene chloride (5 ml) was heated at reflux and the reaction was monitored by tlc until all the nitrile oxide was consumed (30 hours). After evaporation of the solvent the crude reaction mixture was checked by ^{1}H nmr, in which the chemical shifts at δ 7.02 (d, J = 11 Hz) and 5.09 (d, J = 11 Hz) were indicative of isoxazoline **3a**. Separation of the reaction mixture on column chromatography with hexane/ethyl acetate 7:3 as the eluent gave in addition to 2,6-dichlorodiphenylfuroxan and unreacted **1a** the 3-(2,6-dichlorophenyl)-4-(*N*-phenylcarbamoyl)isoxazole (**4a**) 0.15 g (45%), mp 205-207° (from hexane/methylene chloride); ir (nujol): ν 3330 (NH), 1640 (C=O) cm^{-1}; ^{1}H nmr: δ 9.16 (s, 1H), 7.57-7.10 (m, 9H); ^{13}C nmr: δ 162.1, 157.2, 155.5, 136.9, 136.0, 132.7, 132.4,

132.3, 129.1, 128.7, 128.6, 125.0, 120.1; ms: m/z (%) 336/334/332 (M^+, 28), 297/295 (100), 240 (14), 216/214/212 (56), 188/186/184 (27), 93 (42).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.68; H, 3.03; N, 8.41. Found: C, 57.49; H, 2.98; N, 8.32.

Reaction of Isothiazolone **1b** with Nitrile Oxide **2a**.

The same procedure with the former reaction was followed (reflux 10 hours). In the ^1H nmr of the crude reaction mixture the chemical shift at δ 5.98 (s) was indicative of the formation of isoxazoline **3b**. Separation of the reaction mixture by column chromatography with hexane/methylene chloride 1:1 as the eluent gave the 5-benzoyl-3-(2,6-dichlorophenyl)-4-(*N*-phenylcarbamoyl)isoxazole (**4b**) 0.24 g (55%) as yellow crystals, mp 169-171° (from hexane/methylene chloride); ir (nujol): ν 3250, 3190, 3130 (NH), 1675, 1620 (C=O); ^1H nmr: δ 10.88 (s, 1H), 8.17 (d, 2H, J = 7.8 Hz), 7.78-7.58 (m, 5H), 7.46-7.28 (m, 5H), 7.11 (t, 1H, J = 7.4 Hz); ^{13}C nmr: δ 185.3, 162.1, 161.4, 155.9, 137.5, 135.5, 135.2, 135.0, 131.4, 131.0, 129.0, 128.9, 127.9, 127.5, 124.7, 121.3, 120.3; ms: m/z (%) 440/438/436 (M^+, 57), 403/401 (100).

Anal. Calcd. for $C_{23}H_{14}Cl_2N_2O_3$: C, 63.28; H, 3.23; N, 6.42. Found: C, 63.43; H, 3.23; N, 6.63.

Reaction of Isothiazolone **1b** with Nitrile Oxide **2b**.

A solution of **1b** 0.291 g (1 mmole) and **2b** 0.242 g (1.5 mmoles) in dry chloroform (5 ml) was heated at reflux for 15 hours. After evaporation of the solvent the residue was separated by column chromatography with hexane/ethyl acetate 2:1 as eluent to give in addition to mesityl isocyanate compounds **6** 0.09 g (15%) and **5** 0.22 g (50%).

3a,6a-Dihydro-3-mesityl-6a-(3-mesityl-5-phenyl-1,4,2-dioxazol-5-yl)-5-phenyl-isothiazolo[4,5-*d*]isoxazol-4(5*H*)-one (**6**).

This compound was obtained as a mixture of two diastereoisomers (1.5:1), mp 75-80° (from ethanol); ir (nujol): ν 1690 (C=O) cm^{-1}; ^1H nmr: δ 7.89-7.82 (m, 2H), 7.50-7.23 (m, 8H), 6.90, 6.85 and 6.83 (s, 4H), 4.95 and 4.91 (s, 1H), 2.29 (s, 6H), 2.25 and 2.24 (s, 12H); ^{13}C nmr: δ 162.6, 158.1, 158.0, 156.2, 156.0, 141.3, 139.8, 138.9, 138.8, 136.6, 134.1, 130.5, 130.4, 129.3, 129,2, 128.8, 128.7,128.6, 128.3, 128.2, 127.3, 127.2, 127.0, 126.9, 124.1, 123.9, 121.9, 120.0, 118.0, 113.0, 102.3, 102.1, 65.2, 65.1, 21.2, 21.1, 20.2, 20.1, 19.6; ms: m/z (%) 442 (M^+-MesCNO, 10), 281 (11), 161 (100).

Anal. Calcd. for $C_{36}H_{33}N_3O_4S$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.49; H, 5.38; N, 6.81.

5-(3-Mesityl-5-phenyl-1,4,2-dioxazol-5-yl)-2-phenylisothiazol-3(2*H*)-one (**5**).

This compound was obtained as light yellow crystals, mp 150-152° (from hexane/methylene chloride); ir (nujol): ν 1660 (C=O) cm^{-1}; ^1H nmr: δ 7.74-7.28 (m, 10H), 6.91 (s, 2H), 6.38 (s, 1H), 2.30 (s, 3H), 2.26 (s, 6H); ^{13}C nmr: δ 166.7, 157.8, 157.5, 141.4, 138.7, 136.3, 135.8, 130.6, 129.4, 128.8, 128.7, 127.6, 125.7, 124.7, 117.8, 115.5, 110.8, 21.2, 19.8; ms: m/z (%) 442 (M^+, <1), 281 (25), 176 (7), 161 (100), 146 (60), 105 (45).

Anal. Calcd. for $C_{26}H_{22}N_2O_3S$: C, 70.57; H, 5.01; N, 6.33. Found: C, 70.41; H, 5.01; N, 6.28.

REFERENCES AND NOTES

[1] For a survey of the isothiazole and related compounds see D. L. Pain, B. J. Peart and K. R. H. Wooldridge, Comprehensive Heterocyclic Chemistry, Vol **6**, A. R. Katritzky and C. W. Rees eds, Pergamon Press, Oxford, 1984, pp 131-175.

[2] K. F. Burri, *Helv. Chim. Acta*, **72**, 1416 (1989).

[3] A. Waldner, *Helv. Chim. Acta*, **72**, 1435 (1989).

[4] K. F. Burri, *Helv. Chim. Acta*, **73**, 69 (1990).

[5] K. F. Burri, *Chimia*, **46**, 335 (1992).

[6] E. D. Weiler and J. J. Brennan, *J. Heterocyclic Chem.*, **15**, 1299 (1978).

[7] A. Waldner, *Tetrahedron Letters*, **30**, 3061 (1989).

[8] E. Coutouli-Argyropoulou, N. G. Argyropoulos and E. Thessalonikeos, *J. Chem. Res., (S)*, 202, (*M*), 1557 (1990).

[9] N. G. Argyropoulos, E. Coutouli-Argyropoulou and C. Siacavara, *J. Heterocyclic Chem.*, **27**, 2097 (1990).

[10] E. Coutouli-Argyropoulou and E. Thessalonikeos, *Liebigs Ann. Chem.*, 1097 (1990).

[11] P. Grunanger and P. Vita-Finzi, The Chemistry of Heterocyclic Compounds, Vol **49**, E. C. Taylor and A. Weissberger eds, John Wiley and Sons, New York, 1991, p 24.

[12] N. G. Argyropoulos, E. Coutouli-Argyropoulou and P. Pistikopoulos, *J. Chem. Res.*, (S), 362 (1984).

[13] E. Coutouli-Argyropoulou and E. Thessalonikeos, *J. Heterocyclic Chem.*, **28**, 429 (1991).

[14] P. Caramella and P. Grunanger, 1,3-Dipolar Cycloaddition Chemistry, Vol **1**, A. Padwa ed, John Wiley and Sons, New York, 1984, p 359.

[15] N. G. Argyropoulos, N. E. Alexandrou and D. N. Nicolaides, *Tetrahedron Letters*, **17**, 83 (1976).

[16] T. Hayakawa, K. Araki and S. Shiraishi, *Bull. Chem. Soc. Japan*, **57**, 1643 (1984).

[17] A. Tsolomitis and C. Sandris, *J. Heterocyclic Chem.*, **17**, 1645 (1980).

[18] A. Tsolomitis and C. Sandris, *Heterocycles*, **25**, 569 (1987).

[19] C. Grundmann and R. Richter, *J. Org. Chem.*, **33**, 476 (1968).

[20] S. N. Lewis, G. A. Miller, M. Hausman and E. C. Szamborski, *J. Heterocyclic Chem.*, **8**, 571 (1971).