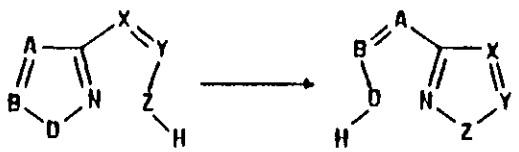
HETEROCYCLIC REARRANGEMENTS. REARRANGEMENTS OF 1,2,4-OXADIAZOLES, ISOXAZOLES, AND 1,2,5-OXADIAZOLES INVOLVING A CARBETHOXYTHIOUREA NCS SEQUENCE

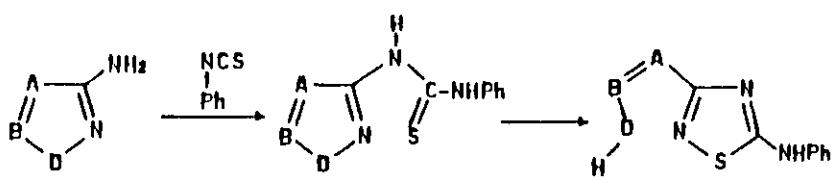
Gabriella Macaluso, Giuseppe Cusmano, Silvestre Buscemi, Vincenzo Frenna, Nicolò Vivona*, and Michele Ruccia
Istituto di Chimica Organica, Università di Palermo,
Via Archirafi 20, 90123 Palermo, Italy

Abstract - The reaction of 3-amino-1,2,4-oxadiazoles **6a,b**, 3-aminoisoxazole **9** and 3-amino-1,2,5-oxadiazoles **12a,b** with ethoxycarbonyl isothiocyanate has been investigated. In the case of **6a,b**, the reaction directly gave the 1,2,4-thiadiazoles **8a,b**, because of a spontaneous rearrangement of the initially formed thioureas **7a,b**. In the case of **9** and **12a,b**, the reaction allowed to isolate the corresponding thioureas which were easily rearranged into 1,2,4-thiadiazoles.

In a previous paper of this series[1] we pointed out that the presence of a sulphur atom in the side chain sequence of **1** (**Z** = **S**) greatly enhances the reactivity of substituted azoles **1** (**ABD** = **NCO**, **CCO**, **CNO**) towards mononuclear heterocyclic rearrangements (**m.h.r.s**) of type **1** ⟶ **2**.[2,3]



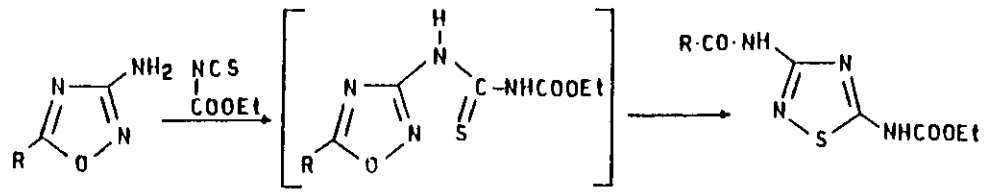
1 **2**



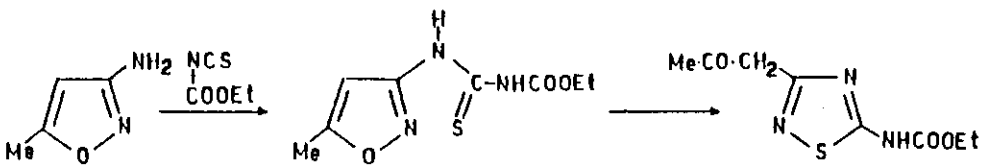
3 **4** **5**

This behaviour was ascribed to the nucleophilic character of the sulphur atom in the reaction involving attack at the ring nitrogen. We also reported[1] that the reaction of 3-amino-1,2,4-oxadiazoles **3** (ABD = NCO) with phenylisothiocyanate directly gave 1,2,4-thiadiazoles **5** (ABD = NCO) through a spontaneous rearrangement of the unisolated thiourea intermediates **4**.

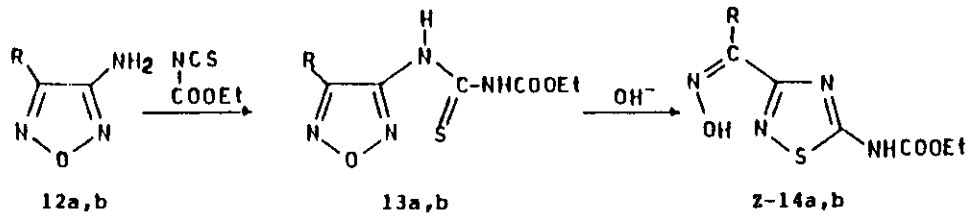
In opposition to this latter result, it was reported[4] that the reaction of 3-amino-5-phenyl-1,2,4-oxadiazole (**6b**) with ethoxycarbonyl isothiocyanate gave the unrearranged thiourea **7b**. In our opinion, owing to the high tendency[3] of the 1,2,4-oxadiazole ring to give a **m.h.r.**, it was foreseen that the initially formed thiourea **7b** should have given a spontaneous rearrangement into the 1,2,4-thiadiazole **8b**.



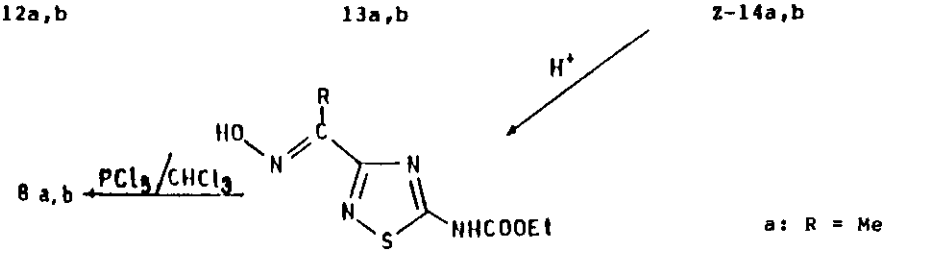
6a,b **7a,b** **8a,b**



9 **10** **11**



12a,b **13a,b** **Z-14a,b**



E-14a,b

a: R = Me

b: R = Ph

In this connection, continuing our researches in this field,[5] we have investigated the reaction of 3-amino-1,2,4-oxadiazoles **6a,b**, 3-aminoisoxazole **9**, and 3-amino-1,2,5-oxadiazoles **12a,b** with ethoxycarbonyl isothiocyanate.

From the reaction between 3-amino-1,2,4-oxadiazoles **6a,b** and ethoxycarbonyl isothiocyanate (performed in different conditions, such as in refluxing ethyl acetate or in DMF at room temperature) we were not able to isolate the thioureas **7a,b**, but we directly obtained the rearrangement products **8a,b**. This indicated that **7**, as soon as formed, readily rearranged into **8**. Therefore, as anticipated,[3] the product obtained from **6b** must be considered the thiadiazole **8b** and not the thiourea **7b**, as reported.[4] Spectral and chemical evidences are in accordance with a rearranged structure for compounds obtained in the reaction. Ir spectrum of **8a** exibits two sharp bands for the C=O stretchings at 1660 and 1710 cm^{-1}, and nmr spectrum showed a singlet at δ 2.05, typical for methyl protons of an acetylamino group rather than for a methyl linked to an heterocyclic ring, as should be expected for **7a**. Acid hydrolysis of **8a** gave the 3-amino-5-carbethoxyamino-1,2,4-thiadiazole,[6] whose benzoylation gave **8b**. Furthermore, the acylamino-1,2,4-thiadiazoles **8a,b** have been also obtained from the Beckmann rearrangement of the E-oximes **E-14a,b** (see below).

As forecast on the basis of our previous findings[1,3] which pointed out a lower tendency of the isoxazole ring to rearrange through a **m.h.r.**, on reacting the 3-aminoisoxazole **9** with ethoxycarbonyl isothiocyanate in ethyl acetate as solvent at room temperature, allowed us to isolate the thiourea **10**. This latter, when treated with bases at room temperature as well as by simple refluxing in ethanol, easily rearranged into the thiadiazole **11**.

In the case of the reaction between 3-amino-1,2,5-oxadiazoles **12a,b** and the isothiocyanate, on refluxing in ethyl acetate or in DMF solution at room temperature, we obtained the expected thioureas **13a,b**. In accordance with the low reactivity of the 1,2,5-oxadiazole ring towards a **m.h.r.** reaction,[1,3] rearrangement of **13** occurred readily at room temperature only in the presence of bases, which enhances the actual nucleophilic character of the sulphur atom of the **NCS** sequence. The rearranged products were the Z-oximes **Z-14**, i.e., with conservation of the geometry present in the starting ring.[1] When refluxed in ethanol in the presence of hydrochloric acid, the Z-oxime **Z-14a** gave the E-oxime **E-14a**, while the Z-oxime **Z-14b** gave a mixture (1:1) of the starting Z-oxime and

the E-oxime **E-14b**. When submitted to the Beckmann rearrangement conditions, the E-oximes **E-14a,b** gave the acylamino-1,2,4-thiadiazoles **8a,b**.

The results obtained agree with our previous findings,[1] and confirm the marked reactivity of the **NCS** side chain sequence in a **m.h.r.** reaction, pointing out the spontaneous rearrangement in the 1,2,4-oxadiazole ring system.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mull) were determined with a Perkin-Elmer 257 instrument; ^{1}H nmr spectra were determined with a Varian EM 360 spectrometer (TMS as internal standard).

Reaction of 3-Amino-1,2,4-oxadiazoles **6a,b** with Ethoxycarbonyl Isothiocyanate.

To a solution of **6a,b** (20 mmoles) in dry DMF (20 ml), ethoxycarbonyl isothiocyanate[7] (25 mmoles) was added and the mixture was allowed to stand at room temperature for 24 hours. In the case of **6a**, the rearrangement product separated. After dilution with water (200 ml), the crude product was filtered off and washed with ethanol (for **6a**), or ethyl acetate (for **6b**) to remove unreacted starting material, yielding the rearrangement products **8a,b** (70%). The same result was obtained in refluxing ethyl acetate as solvent according to the report for **6b**.[4]

Compound **8a** had mp 282-284°C (from dioxane); ir: 3200 and 3100 cm^{-1} (NH), 1710 and 1660 cm^{-1} (CO); ^{1}H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2\underline{CH_3}$), 2.05 (s,3H,$NHCO\underline{CH_3}$), 4.25 (q,2H,$O\underline{CH_2}CH_3$), 10.75 and 12.50 (2s,2H,NH). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.52; H, 4.38; N, 24.34. Found: C, 36.45; H, 4.18; N, 24.44.

Compound **8b** had mp 205-210°C (from ethanol) (lit.[4] mp 197-201°C); ir: 3420, 3220 and 3100 cm^{-1} (NH), 1710-1700 cm^{-1} (CO); ^{1}H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2\underline{CH_3}$), 4.30 (q,2H,$O\underline{CH_2}CH_3$), 7.30-8.10 (m,5H,Ph), 11.20 and 12.60 (br) (2s,2H,NH). Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.14; N, 19.17. Found: C, 49.25; H, 4.10; N, 19.25.

To a suspension of **8a** (1 g) in ethanol (25 ml), hydrochloric acid (36%, 1.5 ml) was added and the mixture was refluxed for 1 hour. Removal of the solvent, addition of water (100 ml) and then aqueous potassium hydroxide (10%, to pH 8-9), gave 3-amino-5-carbethoxyamino-1,2,4-thiadiazole, mp beyond 280°C (lit.[6] mp beyond 250°C). To this crude material (0.5 g) in dry pyridine (6 ml), benzoyl chloride (0.4 ml) was added and the mixture was heated at 100°C for 30 minutes.

Dilution with water (100 ml), filtration and crystallization from ethanol gave 3-benzoylamino-5-carbethoxyamino-1,2,4-thiadiazole (**8b**) (0.4 g), mp 205-210°C.

Reaction of 3-Amino-5-methylisoxazole (**9**) with Ethoxycarbonyl Isothiocyanate.

To a solution of **9** (1 g) in ethyl acetate (10 ml), ethoxycarbonyl isothiocyanate (1.5 ml) was added and the mixture was allowed to stand at room temperature for two hours. Dilution with light petroleum and freezing caused the separation of the thiourea **10** (2 g). Analytical sample (from light petroleum/ethyl acetate on freezing) had mp 114°C; ir: 3145 cm^{-1} (NH), 1730 cm^{-1} (CO), 1200 cm^{-1} (CS); ^1H nmr ($CDCl_3$) δ : 1.35 (t,3H,$OCH_2C\underline{H}_3$), 2.45 (s,3H,CH_3), 4.30 (q,2H,$OC\underline{H}_2CH_3$), 7.05 (s,1H,CH), 8.50 and 11.20 (2s,2H,NH). Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.92; H, 4.84; N, 18.34. Found: C, 42.10; H, 4.80; N, 18.20.

To a solution of **10** (0.6 g) in ethanol (6 ml), aqueous potassium hydroxide (10%, 2 ml) was added. After 10-15 minutes, at room temperature, addition of water (30 ml) and neutralization with acetic acid gave the acetonyl derivative **11** (70%), mp 164°C (from ethanol) (lit.[6] mp 158-160°C); ir: 3160 cm^{-1} (NH), 1720-1710 cm^{-1} (CO); ^1H nmr ($CDCl_3$) δ: 1.40 (t,3H,$OCH_2C\underline{H}_3$), 2.25 (s,3H,$C\underline{H}_3CO$), 4.05 (s,2H,$C\underline{H}_2$), 4.40 (q,2H,$OC\underline{H}_2CH_3$), 10.70 (br s,1H,NH). Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.92; H, 4.84, N, 18.34. Found: C, 42.17; H, 4.98; N, 18.26.

The same rearrangement took also place in the absence of the base, e.g., by refluxing in ethanol for 15-20 minutes.

Reaction of 3-Amino-1,2,5-oxadiazoles **12a,b** with Ethoxycarbonyl Isothiocyanate.

To a solution of **12a,b** (20 mmoles), in dry DMF (10 ml), ethoxycarbonyl isothiocyanate (25 mmoles) was added and the mixture was allowed to stand at room temperature for 24 hours. Dilution with water (200 ml), filtration and crystallization of the crude product from ethanol gave the thioureas **13a,b** (60%).

Compound **13a** had mp 158°C; ir: 3145 cm^{-1} (NH), 1730 cm^{-1} (CO), 1205 cm^{-1} (CS); ^1H nmr ($CDCl_3$) δ : 1.40 (t,3H,$OCH_2C\underline{H}_3$), 2.45 (s,3H,CH_3), 4.30 (q,2H,$OC\underline{H}_2CH_3$), 8.80 and 10.60 (2s,2H,NH). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.52; H, 4.38; N, 24.34. Found: C,36.59; H, 4.47; N, 24.47.

Compound **13b** had mp 160°C; ir: 3125 cm^{-1} (NH), 1720 cm^{-1} (CO), 1200 cm^{-1} (CS); ^1H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2C\underline{H}_3$), 4.25 (q,2H,$OC\underline{H}_2CH_3$), 7.40-7.95 (m,5H,Ph),

10.70 and 11.10 (2s,2H,NH). Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C,49.31; H,4.14; N, 19.17. Found: C, 49.46; H, 4.17; N, 19.26.

Rearrangement of the Thioureas **13.**

To a solution of thioureas **13a,b** (10 mmoles) in ethanol (50 ml) aqueous potassium hydroxide (10%, 15 ml) was added and the mixture was kept at room temperature for 20 hours. Addition of water (200 ml) and neutralization with acetic acid gave the Z-oximes **Z-14a,b** (70%).

Compound **Z-14a** had mp 192-194°C (from ethanol); ir: 3240 cm^{-1} (NH, OH), 1710 cm^{-1} (CO); ^1H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2\underline{CH}_3$), 2.20 (s,3H,CH_3), 4.30 (q,2H,$OC\underline{H}_2CH_3$), 11.80 and 12.50 (br) (2s,2H,NH,OH). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C,36.52; H,4.38; N, 24.34. Found: C, 36.76; H, 4.50; N, 24.10.

Compound **Z-14b** had mp 200-205°C (from ethanol); ir: 3260 and 3150 cm^{-1} (NH,OH), 1725 cm^{-1} (CO); ^1H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2\underline{CH}_3$), 4.30 (q,2H,$OC\underline{H}_2CH_3$), 7.40 (s,5H,Ph), 12.20 and 13.10 (br) (2s,2H,NH,OH). Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C,49.31; H,4.14; N, 19.17. Found: C, 49.21; H, 4.06; N, 19.17.

Isomerization of the Z-Oximes **Z-14a,b.**

A sample of the Z-oxime (2 g), in ethanol (50 ml) and hydrochloric acid (1N, 2 ml) was refluxed 3 hours (for **14a**) or 8 hours (for **14b**). After removing the solvent, the residue was worked up with water (100 ml) and filtered off.

In the case of **14a**, crystallization from ethyl acetate gave the E-oxime **E-14a** (80%), mp 196-198°C; ir: 3320 and 3180 cm^{-1} (NH, OH), 1710 cm^{-1} (CO); ^1H nmr (DMSO) δ : 1.30 (t,3H,$OCH_2\underline{CH}_3$), 2.20 (s,3H,CH_3), 4.30 (q,2H,$OC\underline{H}_2CH_3$), 11.70 and 12.50 (br) (2s,2H,NH,OH). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C,36.52; H,4.38; N, 24.34. Found: C, 36.31; H, 4.25; N, 24.07

In the case of **14b**, the mixture was chromatographed on dry column of Merk silica-gel (300 g) deactivated with water (15%). Elution with cyclohexane-ethyl acetate (4:1), first removed some amounts of hydrolysis products (discarded) and then the starting Z-oxime (0.7 g). Elution with ethyl acetate gave the E-oxime **E-14b** (0.7 g), mp 178-180°C (from benzene); ir: 3220 cm^{-1} (NH,OH), 1715 cm^{-1} (CO); ^1H nmr (DMSO) δ: 1.30 (t,3H,$OCH_2\underline{CH}_3$), 4.25 (q,2H,$OC\underline{H}_2CH_3$), 7.35 (s,5H,Ph), 11.80 (br s,2H,NH,OH). Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C,49.31; H,4.14; N, 19.17. Found: C, 49.67; H, 4.09; N, 19.38.

Beckmann Rearrangement of the E-Oximes **E-14a,b.**

To a sample of the E-oxime (5 mmoles) in dry chloroform (60 ml), cooled in an ice bath, phosphorous pentachloride (10 mmoles) was added. The mixture was kept at room temperature for 15 hours and then the solvent allowed to evaporate spontaneously at room temperature.

In the case of **E-14a** the residue was worked up with the minimum amount of ethanol, followed by addition of water (50 ml). After neutralization with ammonium hydroxide, the crude product was filtered off, refluxed in ethanol (50 ml), and filtered again. The insoluble fraction, after crystallization from dioxane, gave **8a** (35%).

In the case of **E-14b**, working up with ethanol/water and filtration gave a crude material, which was crystallized from ethanol giving **8b** (40%).

ACKNOWLEDGEMENTS

We thank Ministero P.I. (Rome) for support.

REFERENCES

1. N. Vivona, G. Cusmano, and G. Macaluso, J. Chem. Soc. Perkin Trans. 1, 1977, 1616.
2. A. J. Boulton, A. R. Katritzky, and A. M. Hamid, J. Chem. Soc. (C), 1967, 2005.
3. M. Ruccia, N. Vivona, and D. Spinelli, Adv. Heterocycl. Chem., 1981, 29, 141.
4. G. Westphal and R. Schmidt, Z. Chem., 1974, 14, 94; Chem. Abstr. 1974, 81, 13445.
5. N. Vivona, S. Buscemi, V. Frenna, and M. Ruccia, J. Chem. Soc. Perkin Trans.1, 1986, 17; and references cited therein.
6. B. Koren, B. Stanovnik, and M. Tisler, J. Heterocycl. Chem. 1977, 14, 621.
7. R. Esmail and F.Kurzer, Synthesis, 1975, 301.

Received, 16th July, 1986