Pergamon

Tetrahedron 57 (2001) 5455–5459

TETRAHEDRON

Isothiazoles. Part 12: Isothiazolylphosphonates, a new class of isothiazole dioxides

Francesca Clerici,* Maria Luisa Gelmi, Elena Pini and Marinella Valle

Facoltà di Farmacia e Centro Interuniversitario di Ricerca sulle Reazioni Pericicliche e Sintesi di Sistemi Etero e Carbociclici, Istituto di Chimica Organica, Università di Milano, Via Venezian 21, 20133 Milano, Italy

Received 22 February 2001; revised 4 April 2001; accepted 20 April 2001

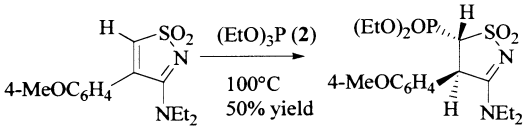
Abstract—We describe a mild and efficient method to prepare 3-amino-4,5-dihydro-5-isothiazolylphosphonates from 3-amino-5-unsubstituted isothiazole dioxides. Starting from 3-amino-5-bromo-isothiazole dioxides either 3-amino-5-isothiazolylphosphonates or 5-diethoxyphosphoryl-4,5-dihydro-4-isothiazolylphosphonates were prepared. Isothiazolylphosphonates represent a new class of isothiazole dioxides. Some preliminary investigations on the reactivity with 1,3-dipoles were reported.

1. Introduction

It is known that the phosphono group is largely present in natural compounds, frequently regulating very important biological functions. Furthermore, several phosphonate derivatives exhibit various pharmaceutical and phyto-pharmaceutical activities, as well as rheological properties of interest for different industrial applications. Thus a large number of new phosphonic acids and their derivatives have been prepared hitherto with special attention to heterocyclic compounds.[1–4] In consideration with this fact and in continuing our research on the reactivity of 3-amino-4-aryl-isothiazole 1,1-dioxides,[5,6] we attempted to prepare isothiazol 1,1-dioxides functionalized with the phosphonate group and to study their reactivity.

2. Results and discussion

3-Diethylamino-4-(4-methoxyphenyl)isothiazol 1,1-dioxide **1a** was reacted with triethylphosphite (TEP, **2**) as the solvent at 100°C to give compound **3** as the sole reaction product in 50% yield (Scheme 1).



1a **3**

Scheme 1.

The structure of compound **3** was confirmed by analytical and spectroscopic data showing the characteristic signals associated with the ethoxy groups linked to the phosphorus atom (two overlapped triplets at 1.35 δ associated with the methyl groups, two quartets at 4.15, 4.25 δ associated with the CH_2O groups) and two double doublets at 3.70 and 4.75 δ associated with H-4 and H-5, respectively (J_{H4-P}=16.5 Hz; J_{H5-P}=17.8 Hz). The small coupling constant (J_{H-H}=3.3 Hz) indicates a *trans* configuration according to the less steric hindrance between the bulky aromatic and phosphonate groups. The ^{13}C NMR spectrum is mainly characterized by a singlet at 52.5 δ which is associated with C-4 and by a doublet at 64.9 δ ($^1J_{C-P}$=141.2 Hz) associated with C-5. A long range coupling with phosphorus was observed also for C-3 (166.2 δ, $^3J_{C-P}$=5.5 Hz). The correct assignment was confirmed by performing $^{13}C-^1H$ correlation experiments which showed an evident relation between the signals at 4.75 and 3.70 δ with those at 64.9 and 52.5 δ, respectively.

Compound **3** is formed through nucleophilic attack of TEP on C-5 that has been previously demonstrated to be the more electrophilic center of the isothiazole dioxide ring.[7]

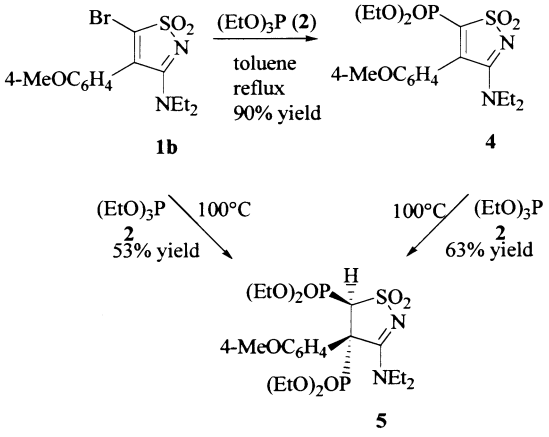
When the reaction was performed on **1b** in toluene and with an equimolecular amount of TEP (**2**) compound **4** was obtained through an addition–elimination process. This latter was transformed into **5** by reacting with TEP (**2**) as the solvent at 110°C. The same product, i.e. could be obtained directly by heating **1b** in TEP (**2**) as the solvent at 110°C for 4 h (Scheme 2).

The structures of compounds **4** and **5** were confirmed by analytical and spectroscopic data. Particularly for compound **5** ^1H NMR and ^{13}C NMR analyses were very helpful to ascertain the correct regiochemistry of the TEP

Keywords: isothiazoles; phosphonates; sulfur heterocycles; cycloaddition reactions.

* Corresponding author. Tel.: +39-2-706-303-48; fax: +39-2-706-384-73; e-mail: francesca.clerici@unimi.it

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00448-3



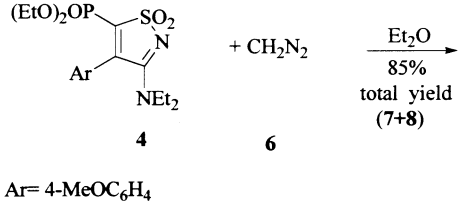
Scheme 2.

addition. In the ^{1}H NMR spectrum a double doublet at 4.6 δ, showing two coupling constants approximately in the same range ($^{2}J_{H-P}$=19.4 Hz, $^{3}J_{H-P}$=23 Hz), was associated with H-5. This signal appeared as a singlet in the $^{1}H-^{31}P$ decoupled spectrum. The most relevant features in the ^{13}C NMR spectrum are two doublets at 64.0 and at 64.8 Hz both showing a very large coupling constant $^{13}C-^{31}P$ (^{1}J=138, 152 Hz, respectively) which is consistent with a coupling via one bond with the phosphorus confirming that both carbons were directly linked to a phosphonate group. The stereochemistry was assigned on the basis of NOE experiments taking into account the lack of Overhauser effects between H-5 and the hydrogens of the 4-methoxysubstituted aryl group.

Compound **5** was evidently formed by virtue of a nucleophilic attack of TEP on C-4 in the intermediate **4**, showing a reversal of the regiochemistry of the nucleophilic addition compared with **1a** and **1b** and, in general, of 3-amino-isothiazole dioxides. This result prompted us to investigate the reactivity of **4** in 1,3-dipolar cycloaddition reaction.

Isothiazolylphosphonate **4** readily reacted with an ethereal solution of diazomethane (**6**) affording a mixture of the two tautomeric 1- and 2-pyrazolines **7** and **8** (Scheme 3). The 1-pyrazoline **7**, which is the primary cycloadduct, tautomerizes at a slower rate into the more stable 2-pyrazoline **8**. This latter was obtained in high yield in pure form while **7** was obtained in minor amount and always in mixture with **8**. This result gives good evidence that the cycloaddition reaction is easy and highly regioselective.

The structure of compounds **7** and **8** were confirmed by analytical and spectroscopic data. NOESY experiments were performed to ascertain the regiochemistry of the cycloaddition and the conclusion confirmed by safe determination of the structure of the transformation products (see later). It is worth noting that unsubstituted, alkyl- and aryl-substituted-isothiazole dioxides are known to react with diazomethane in a highly sito- and regio-selective manner, affording the pyrazoline with a opposite regiochemistry compared to **7** and **8**.[8] Both the theoretical and practical results of cycloadditions of diazoalkanes to electron-deficient double bonds suggest that in most cases the simple rules hold that the dipolar carbon links to the dipolarophile site having the greater electron deficiency. In line with this, our results suggest that in the isothiazolylphosphonate ring a charge distribution exists according to which the more electrophilic center is located on C-4. It has to be noted that this picture fits well with the formation of compound **5**, nucleophilic addition of TEP (**2**) occurring at C-4 of **4**.

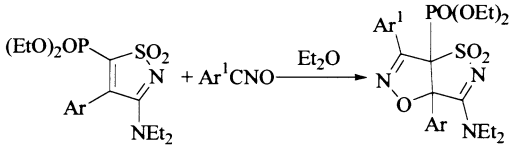


Ar= 4-MeOC$_6$H$_4$

Scheme 3.

Those results prompted us to investigate another class of 1,3-dipoles, viz. the nitrile oxides (Scheme 4). Previously, we demonstrated that 5-unsubstituted 3-amino-isothiazole dioxides act as good dipolarophiles in cycloaddition reactions with nitrile oxides affording isothiazolo[5,4-*d*]-isoxazole derivatives.[9] In this case, the cycloaddition reaction was performed with 4-methoxybenzonitrile oxide **9a** and 4-chlorobenzonitrile oxide **9b** which were generated in situ according to literature method.[10,11] The structures of compounds **10** were confirmed by analytical and spectroscopic data which allowed to assign the correct regiochemistry. In this case, the products **10a** and **10b** showed a regiochemistry in accordance with a charge-controlled cycloaddition reaction. The reaction is highly regioselective only one regioisomer **10a** or **10b** being detected at least at the detection limits (^{1}H NMR, TLC on the whole reaction mixture).

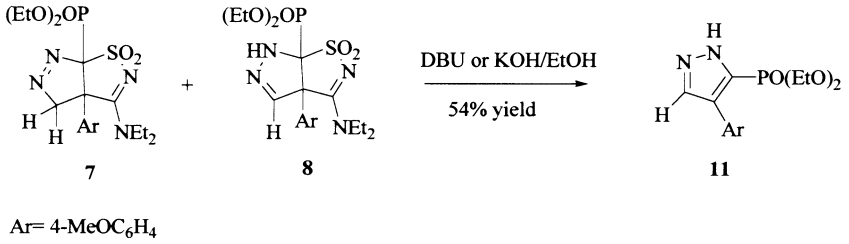
Compounds **8** and **10** were stable at room temperature but underwent rapid decomposition when heated with bases (ethanolic KOH at reflux or DBU at 100°C). Compound **8**



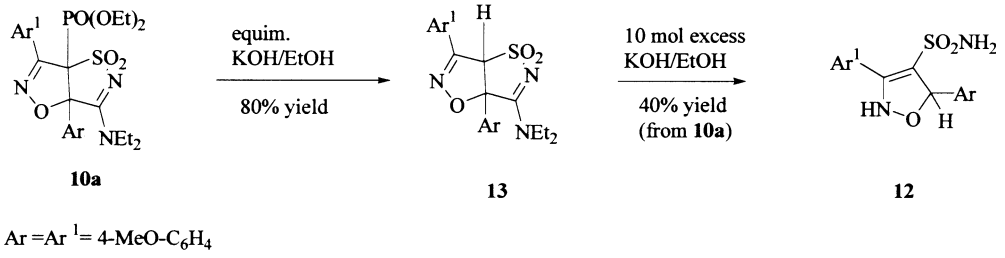
Ar= 4-MeOC$_6$H$_4$

9,10a Ar^1= 4-MeO-C$_6$H$_4$ 65% yield
9,10b Ar^1= 4-Cl-C$_6$H$_4$ 65% yield

Scheme 4.



Scheme 5.



Scheme 6.

afforded pyrazolylphosphonate **11** through a base-catalyzed elimination reaction of SO_2 and diethylcyanamide with cleavage of the isothiazole dioxide ring according to a documented general trend (Scheme 5).[12–14] **10a** treated with DBU afforded a complex mixture of intractable tars. By treatment with an excess of ethanolic KOH compounds **12** was found. The transformation to isoxazole **12** occurred through initial elimination of the phosphonate group leading to **13**.[9] This was confirmed by reacting **10a** with an equimolecular amount of ethanolic KOH: in this conditions only **13** was isolated from the reaction mixture which was transformed into **12** by reacting with an excess of the base (Scheme 6).

By a simple and mild method we made available compounds **3**, **4**, **5** which displayed an isothiazole dioxide moiety substituted with one or two phosphono groups that appeared to be new classes of isothiazole 1,1-dioxides. On this basis, we planned a study of the chemical reactivity of these new class of compounds. Compound **4** was demonstrated to be a good partner in 1,3-dipolar cycloaddition reactions with diazomethane and nitrile-oxides, affording byciclic systems which are susceptible to cleavage to pyrazolylphosphonate and isoxazolylsulfonamide, respectively.

3. Experimental

^{1}H NMR spectra were obtained in $CDCl_3$ as the solvent 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. Compounds **1a**,[15] **b**,[16] **6**[17] have already been described. Nitrile oxide **9a** was generated in situ according to published procedures.[10] 4-Chlorobenzonitrile oxide **9b** was obtained by dehydrohalogenation of the hydroximoyl chloride in diethyl ether (colorless crystals, mp 82–83°C).[11]

3.1. Data for compounds

3.1.1. [3-Diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-1*H*-isothiazol-5-yl]-phosphonic acid diethyl ester 3. Compound **1a** (3.4 mmol) was suspended in $(EtO)_3P$ **2** (10 mL) and heated under stirring at 100°C until disappearance of the starting material (4 h, TLC AcOEt/toluene 9:1). The solvent was evaporated i.v. and the residue chromatographed on silica gel (cyclohexane/AcOEt 100:0 to 0:100) affording **3**. Yield 50%. Mp 106°C (white powder from diethyl ether). IR (nujol) cm^{-1} 1590 (C═N), 1260–1240 (P═O), 1050 (P–O); ^{1}H NMR 0.87 (t, 3H, J=7.2 Hz, CH_3); 1.20 (t, 3H, J=7.2 Hz, CH_3); 1.30 (2t, J=7.1 Hz, 6H, CH_3); 3.06–3.19 (m, 1H, CH_2); 3.38–3.45 (m, 1H, CH_2); 3.62–3.68 (m, 2H, CH_2); 3.70 (dd, 1H, J_{H-H}=3.3 Hz, J_{H4-P}=16.5 Hz, H_4); 3.80 (s, 3H, OCH_3); 4.15, 4.25 (2q, J=7.1 Hz, 4H, CH_2); 4.75 (dd, 1H, J_{H-H}=3.3 Hz, J_{H5-P}=17.8 Hz, H_5); 6.8 (AB syst., J_{AB}=8.7 Hz, 2H, aryl-H); 7.2 (AB syst., 2H, J_{AB}=8.7 Hz, aryl-H). ^{13}C NMR 12.1, 13.4, 16.6–16.8, 43.5, 45.0, 52.5, 55.7, 63.7, 64.8, 64.9, 115.4, 128.7, 129.7, 160.0, 166.2. ^{31}P NMR 15.90. Calcd for $C_{18}H_{29}N_2O_6PS$ (432.47) C 49.99 H 6.76 N 6.48, found C 50.36 H 6.80 N 6.18. *m/z* 433 (M^+).

3.1.2. [3-Diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-*1*H-isothiazol-5-yl]-phosphonic acid diethyl ester 4. Compound **1b** (0.27 mmol) was suspended in toluene (5 mL) and $(EtO)_3P$ **2** (0.81 mmol, 135 μL) was added and the mixture heated at reflux until disappearance of the starting material (2 h, TLC AcOEt/toluene 9:1). The solvent was evaporated under reduced pressure and the residue slowly crystallized from diethylether affording **4**. Yield 90%. Mp 96°C (pale yellow powder from diethyl ether). IR (nujol) cm^{-1} 1603, 1570 (C═C, C═N), 1245 (P═O), 1055 (P–O); ^{1}H NMR 0.87–0.89 (m, 3H, CH_3); 1.20–1.41 (m, 9H, CH_3); 2.97–3.17 (m, 2H, CH_2); 3.50–3.75 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3); 4.06–4.24 (m, 4H, CH_2); 6.8 (AB syst., 2H, J_{AB}=8.7, aryl-H,); 7.2 (AB syst., 2H, J_{AB}=8.7,

aryl-H,). ^{13}C NMR 11.7, 14.2, 16.1–16.2, 44.0, 47.5, 55.4, 63.8, 114.3, 122.3, 128.7, 132.8, 146.0, 159.0, 160.8. ^{31}P NMR 1.93. Calcd for $C_{18}H_{27}N_2O_6PS$ (430.46) C 50.22 H 6.32 N 6.51 found C 50.80 H 6.73 N 6.60.

3.1.3. [5-(Diethoxy-phosphoryl)-3-diethylamino-4-(4-methoxyphenyl)-1,1-dioxo-4,5-dihydro-isothiazol-4-yl] phosphonic acid diethyl ester 5. *Method A*: Compound **1b** (0.27 mmol) was suspended in $(EtO)_3P$ **2** (5 mL) and heated under stirring at 100°C until disappearance of the starting material (4 h, TLC AcOEt/toluene 9:1). The solvent was evaporated i.v. and the residue chromatographed on silica gel (cyclohexane/AcOEt 100:0 to 0:100) affording **5**. Yield 53%. *Method B*: Compound **4** (0.22 mmol) was suspended in $(EtO)_3P$ **2** (5 mL) and heated under stirring at 110°C until disappearance of the starting material (4 h, TLC AcOEt/toluene 9:1). The solvent was evaporated i.v. and the residue chromatographed on silica gel (cyclohexane/AcOEt 100:0 to 0:100) affording **5**. Yield 63%. Mp 151°C (white powder from diethylether). IR (nujol) cm^{-1} 1570 (C═N); 1250 (P═O); 1020(P–O); ^{1}H NMR 0.85, 1.13, 1.23, 1.26, 1.36, 1.45 (6t, 18H, J=7 Hz, CH_3); 3.05, 3.31, 3.50, 3.65 (4m, 4H, $2CH_2$); 3.79 (s, 3H, OCH_3); 3.70–3.99, 4.15–4.30 (2m, 6H, $3CH_2$); 4.45 (q, 2H, J=7 Hz, CH_2); 4.60 (dd, $^2J_{H-P} \cong {}^3J_{H-P}$, 19.34 and 22.95 Hz, 1H, H-5,); 6.87 (d, AB syst., 2H, J=8.8 Hz, aryl-H); 7.25 (bs, 1H, aryl-H); 7.60 (bs, 1H, aryl-H). ^{13}C NMR 11.6, 13.0, 16.4–16.18, 46.0, 46.1, 55.7, 63.3, 64.0, 64.6, 64.7, 64.8, 114.0, 124.0, 129.7, 160.0, 163.7. ^{31}P NMR 12.0 (d, 1P, J_{P-P}=11.9), 19.0 (d, 1P, J_{P-P}=11.9). Calcd for $C_{22}H_{38}N_2O_9$ P_2S (568.56) C 46.67 H 6.74 N 4.93, found C 47.02 H 6.42 N 4.74.

3.1.4. Cycloaddition reaction of 4 and diazomethane 6. Compound **4** (0.23 mmol) was dissolved in toluene (5 mL) and a ethereal solution of diazomethane **6** was slowly dropped in under stirring at room temperature. After 1 h the reagent has completely disappeared (TLC AcOEt/toluene 9:1). Evaporation of the solvent and crystallization from diethyl ether afforded **7** and **8** in mixture. By stirring the mixture in chloroform solution, **7** was completely transformed into **8**. Total yield (**7**+**8**) 85%.

3.1.5. [3-Diethylamino-3*a*-(4-methoxyphenyl)-1,1-dioxo-3*a*,6*a*-dihydro-pyrazolo[4,3-*d*]isothiazol-6*a*-yl] phosphonic acid diethyl ester 8. Mp 141–143°C (white powder from diethyl ether). IR (nujol) cm^{-1} 3280–3230 (NH); 1586 (C═N); 1236 (P═O); 1023(P–O); ^{1}H NMR 0.90 (t, 3H, J=7.1 Hz, CH_3); 1.10–1.22 (m, 9H, CH_3); 2.89–3.15 (m, 2H, CH_2); 3.34–3.54 (m, 2H, CH_2); 3.82 (s, 3H, OCH_3); 3.84–4.05 (m, 4H, CH_2); 6.47 (d, J_{H-P}=2.61 Hz, NH); 6.88–7.00 (m, 3H, aryl-H+H-4); 7.16 (d, AB syst., 1H, J_{AB}=8.8 Hz, aryl-H); 7.73 (d, AB syst., J_{AB}=8.8 Hz, 1H, aryl-H). ^{13}C NMR 11.3, 12.6, 16.1–16.3, 43.1–44.8, 55.4, 64.0, 64.1, 81.5, 83.3, 114.1, 124.7, 128.3, 129.5, 137.4, 160.6, 166.0. ^{31}P NMR 8.8. Calcd for $C_{19}H_{29}N_4O_6PS$ (472.50) C 48.30 H 6.19 N 11.86 found C 48.46 H 6.15 N 11.54.

3.1.6. [3-Diethylamino-3*a*-(4-methoxyphenyl)-1,1-dioxo-3*a*,4-dihydro-pyrazolo[4,3-*d*]isothiazol-6*a*-yl]phosphonic acid diethyl ester 7. Compound **7** was always obtained in mixture with **8**. In the ^{1}H NMR spectrum of the mixture significant signals are: 5.40 (dd, 1H, J=20.2 Hz, J_{H-P}=13.9 Hz); 5.85 (dd, 1H, J=20.2 Hz, J_{H-P}=16 Hz); ^{13}C NMR 70.7 (C6*a*); ^{31}P NMR 14.29.

3.1.7. [6-Diethylamino-3*a*,6*a*-dihydro-4,4-dioxo-3,6*a*-di-(4-methoxyphenyl)-isothiazolo-[5,4-*d*]-isoxazol-3*a*-yl]-phosphonic acid diethyl ester 10a. Compound **4** (0.96 mmol) was dissolved in ethanol (10 mL) and 4-methoxybenzaldoxime (0.96 mmol) and chloramine T (1.5 mmol) were added in one portion. The mixture was refluxed until disappearance of the starting materials (2 h, TLC AcOEt). The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel (cyclohexane/AcOEt 100:0 to 0:100) affording pure **10a**. Yield 65%. Mp142–143°C (white powder from diethyl ether). IR (nujol) cm^{-1} 1610, 1520; 1260 (P═O); 1050(P–O); ^{1}H NMR 0.95, 1.05, 1.14, 1.26 (4t, 12H, J=7 Hz, CH_3); 2.90–3.05 (m, 2H, CH_2); 3.20–3.45 (m, 2H, CH_2); 3.65–4.20 (m, 4H, CH_2); 3.86 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 6.87–7.02 (m, 2H, aryl-H); 6.92 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.10–7.20 (m, 1H, aryl-H); 7.65–7.80 (m, 1H, aryl-H); 8.30 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H). ^{13}C NMR 11.14, 12.93, 16.00, 43.64, 45.27, 55.31, 55.44, 63.50, 63.65, 64.51, 64.65, 84.14, 101.80, 113.23, 113.75, 113.92, 119.77, 123.99, 128.47, 128.76, 132.55, 155.15, 161.20, 165.40. ^{31}P NMR 8.93. Calcd for $C_{26}H_{34}N_3O_8PS$ (579.60) C 53.88 H 5.91 N 7.25, found 54.20 H 6.28 N 6.90.

3.1.8. [3-(4-Chlorophenyl)-6-diethylamino-3*a*,6*a*-dihydro-4,4-dioxo-6*a*-(4-methoxyphenyl)-isothiazolo-[5,4-*d*]-isoxazol-3*a*-yl]-phosphonic acid diethyl ester 10b. A benzene solution of the hydroximoyl chloride (0.23 mmol) was dropped into a stirred solution of triethylamine (0.23 mmol) in the same solvent at 0°C. After a few minutes the mixture was allowed to warm to room temperature and a solution of **4** (0.23 mmol) in benzene (2 mL) and dichloromethane (1 mL) was added dropwise. At the end of the addition the mixture was refluxed until disappearance of the reactants (about 8 h, TLC AcOEt/toluene 9:1). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (cyclohexane/AcOEt 100:0 to 0:100) affording **10b**. Yield 65%. Mp 130°C (white powder from diethyl ether). IR (nujol) cm^{-1} 1610, 1520; 1260 (P═O); 1050(P–O); ^{1}H NMR 0.95, 0.96, 1.05, 1.14 (4t, 12H, J=6.9 Hz, CH_3); 2.85–3.10, 3.15–3.45, 3.60–4.10 (3m, 8H, $4CH_2$); 3.87 (s, 3H, OCH_3); 6.90–7.05 (m, 2H); 7.10–7.20 (m, 1H); 7.37 (d, AB syst., 2H, J_{AB}=8.8); 7.69–7.80 (m, 1H); 8.28 (d, AB syst., 2H, J_{AB}=8.8). ^{13}C NMR 11.14, 12.91, 15.96, 16.07, 43.69, 45.34, 55.46, 63.58, 63.72, 64.70, 64.81, 84.00, 102.18, 113.90, 123.55, 126.02, 128.04, 128.36, 128.70, 132.18, 136.86, 154.85, 161.08, 165.10. Calcd for $C_{25}H_{31}N_3ClO_7PS$ (584.02) C 51.41 H 5.35 N 7.19, found C 51.48 H 5.19 N 7.35.

3.1.9. 4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-yl)phosphonic acid diethyl ester 11. Compound **8** (0.21 mmol) was heated at 100°C with an equimolecular amount of DBU (0.21 mmol, 31 μL) and the reaction checked by TLC (1 h, AcOEt/toluene 9:1). The reaction mixture was taken up with dichloromethane and washed with HCl 10%(1 mL) and then with water (2×1 mL). The organic layer was separated, dried over Na_2SO_4, filterd and the

solvent evaporated under reduced pressure affording **11**. Yield 54%. Mp 84°C (pale yellow powder from pentane). IR (nujol) cm^{-1} 3100–3000 (NH); 1610; 1245 (P=O); 1010 (P–O). ^1H NMR 1.23 (t, 6H, J=7.1 Hz, CH_3); 3.87 (s, 3H, OCH_3); 4.06 (q, 4H, J=7.1 Hz, CH_2); 6.97 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.77 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.98 (s, 1H, CH); 8.83 (bs, 1H, NH, exch. D_2O). ^{13}C NMR 16.1, 16.2, 55.3, 62.1, 62.2, 103.5, 113.9, 123.1, 129.1, 141.6, 150.2, 160.3. ^{31}P NMR 16.09. Calcd for $C_{14}H_{19}N_2O_4P$ (310.29) C 54.19 H 6.17 N 9.03 found C 53.42 H 6.08 N 8.80.

3.1.10. 3,5-Bis-(4-methoxyphenyl)-2,5-dihydro-isoxazole-4-sulfonic acid amide 12. Compound **10a** (0.69 mmol) was dissolved in ethanol (8 mL) and a solution of KOH (0.386 mg, 6.9 mmol) in ethanol (10 mL) was added in one portion. The reaction mixture was refluxed until disappearance of the starting material (16 h, TLC AcOEt/cyclohexane 1:1 or CH_2Cl_2/MeOH 10:1). The solvent was evaporated under reduced pressure and the residue acidified with 10% HCl to congo red and extracted in dichloromethane (10 mL). The organic phase was washed with water (2×5 mL), separated, dried with Na_2SO_4, filtered and the solvent evaporated under reduced pressure affording impure **12** which was purified by column chromatography (CH_2Cl_2/MeOH 5:1). Yield: 40%. Mp 167–168°C (white powder from diethyl ether). IR (nujol) cm^{-1} 3420, 3306 (NH). ^1H NMR (DMSO) 3.78 (s, 3H, CH_3); 3.81 (s, 3H, CH_3); 5.84 (s, 1H, H-5); 6.30–6.40 (bm, 3H, NH+NH_2, exch. D_2O); 6.90 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.00 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.45 (d, AB syst., 2H, J_{AB}=8.8 Hz, aryl-H); 7.75 (d, AB syst., 2H, J_{AB}=8.8, aryl-H). ^{13}C NMR (DMSO) 55.01, 55.28, 72.38, 113.5, 113.8, 121.0, 126.4, 128.4, 129.4, 137.0, 155.1, 159.0, 160.6. Calcd for $C_{17}H_{18}N_2O_5S$ (362.40) C 56.34 H 5.01 N 7.73, found C 56.47 H 4.95 N 7.99.

3.1.11. [6-Diethylamino-3*a*,6*a*-dihydro-3*a*,6*a*-di-(4-methoxyphenyl)-isothiazolo-[5,4-*d*]-isoxazole]-4,4-dioxide 13. Compound **10a** (0.18 mmol) was dissolved in ethanol (5 mL) and a solution of KOH (10.1 mg, 0.18 mmol) in ethanol (1.0 mL) was added in one portion and stirred until disappearance of the starting material (3 h, TLC AcOEt/cyclohexane 1:1 or CH_2Cl_2/MeOH 10:1). The solvent was evaporated under reduced pressure and the residue acidified with 10% HCl to Congo red and extracted in dichloromethane (5 mL). The organic phase was washed with water (2×2.5 mL), separated, dried with Na_2SO_4, filtered and the solvent evaporated under reduced pressure affording **13**. Yield: 80%. Mp 168°C (lit.[9] 169–170°C).

References

1. Matoba, K.; Yonemoto, H.; Fukui, M.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 3918–3925.
2. Shen, Y.; Zheng, J.; Xin, Y.; Lin, Y.; Qi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 997–999.
3. Lu, R.; Yang, H. *Tetrahedron Lett.* **1997**, *38*, 5201–5204.
4. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
5. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **2000**, *56*, 4817–4821 and references cited therein.
6. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 14975–14984.
7. Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 2001–2012.
8. Clerici, F.; Ferrario, T.; Gelmi, M. L.; Marelli, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2533–2536.
9. Clerici, F.; Ferraris, F.; Gelmi, M. L. *Tetrahedron* **1995**, *51*, 12351–12362.
10. Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, *1*, 57–59.
11. Grundman, C.; Grünanger, P. In *The Nitrile Oxides*; Springer: Berlin, 1971; pp 44.
12. Baggi, P.; Clerici, F.; Gelmi, M. L.; Mottadelli, S. *Tetrahedron* **1995**, *51*, 2455–2466.
13. Clerici, F.; Galletti, F.; Pocar, D.; Roversi, P. *Tetrahedron* **1996**, *52*, 7183–7200.
14. Clerici, F.; Gelmi, M. L.; Soave, R.; Valle, M. *Tetrahedron* **1998**, *54*, 11285–11296.
15. Clerici, F.; Marazzi, G.; Taglietti, M. *Tetrahedron* **1992**, *48*, 3227–3238.
16. Clerici, F.; Erba, E.; Gelmi, M. L.; Valle, M. *Tetrahedron* **1997**, *53*, 15859–15866.
17. Vogel, A. In *Textbook of Practical Organic Chemistry*; 4th ed., Longman: New York, 1978; pp 291.