Tetrahedron Vol. 41, No. 24, pp. 5989 to 5994, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

REACTION OF ACYLAMINOCYANOESTERS WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-DISULFIDE LEADING TO SUBSTITUTED AMINOTHIAZOLES. CRYSTAL STRUCTURE OF 5-AMINOTHIAZOLE-4-CARBOXYLIC ACID ETHYL ESTER.

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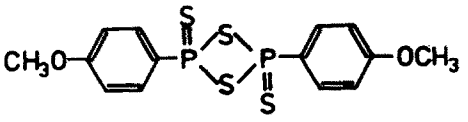
(*Received in UK* 12 *August* 1985)

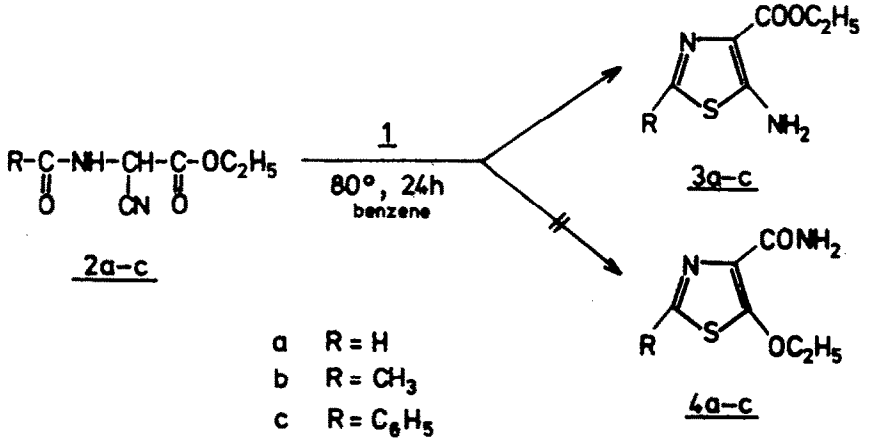
Abstract - 2-Acylamino-2-cyanoacetic acid ethyl esters 2a-c react with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide 1 in refluxing benzene with formation of 2-alkyl(aryl)-5-aminothiazole-4-carboxylic acid ethyl esters 3a-c. Structure 3 was established by spectroscopic means and an X ray crystallographic investigation of 3a. X-Ray analysis revealed that the thiazole ring, exocyclic nitrogen and carbonyl group forming a hydrogen-bonded cycle are nearly coplanar. A resonance interaction is manifested by distinctly shortened /1.447(3)Å/ $C_{(carbonyl)}-C_{(thiazole)}$ distance.

It has been demonstrated that 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide 1 is a very effective thiation reagent for a great variety of carbonyl compounds[1-4]. Some other reactions of 1 with carbonyl compounds like formation of various phosphorus heterocycles[1,5-10], thiadiazoles[6,10], thiophenes[10] and thiazoles[10] have also been noted.



1

We observed a novel ring closure reaction effected by 1. On the attempt of thiation of 2-formylamino-2-cyanoacetic acid ethyl ester 2a, and the respective 2-acetyl compound 2b, with 1 in refluxing anhydrous benzene, 5-aminothiazole-4-carboxylic acid ethyl ester 3a and its 2-methyl derivative 3b were formed.



2a-c

3a-c

4a-c

a R = H
b R = CH_3
c R = C_6H_5

Structure 3 was derived from microanalyses, MS, IR, ^1H and ^{13}C NMR spectroscopic data (Tables 1-3) and X-ray crystallographic investigation of 3a. In contrast to the mass spectra of parent compounds 2a and 2b which were devoid of molecular ions, intensive molecular ions with m/z indicating the replacement of an oxygen atom by a sulphur one, were present in the mass spectra of the thiation products.

Table 1

Experimental, physical, analytical and mass spectral data for 5-amino-2R-thiazole-4-carboxylic acid ethyl esters 3.

	Mp°C Found	Mp°C Reported	Yield %	Empirical Formula	Analyses Calcd / Found C	H	N	S	Mass spectrum m/z (rel.abund %) M^+	$M-46^+$	
3a	163	162-63[11]	70	$C_6H_8N_2O_2S$	41.86	4.65	16.28	18.60	172	126	
					41,95	4.63	16.18	18.44	(59.2)	(100)	
3b	158	156-57[12]	32	$C_7H_{10}N_2O_2S$	45.16	5.38	15.05	17.20	186	140	
					45.17	5.37	14.95	17.25	(99.8)	(100)	
3c	136	-	10	$C_{12}H_{12}N_2O_2S$	58.07	4.83	11.29	12.92	248	202	121
					57.64	4.73	11.43	12.75	(55.8)	(41.6)	(100)

Table 2

IR spectral data for 2 and 3 (cm^{-1}, KBr)

	νNH_2	νNH	νCN	ν ester C=O	ν amide C=O
2a	-	3305	2270	1740	1670
2b	-	3290	2255	1740	1650
2c	-	3250	2250	1743	1642
3a	3400	-	-	1675	-
3b	3420	-	-	1670	-
3c	3400	-	-	1665	-

Already from the IR spectra it was evident that the action of 1 did not result in a simple C=O to C=S conversion, but involved also the cyano group and the vicinity of the ester carbonyl. The disappearance of the original C=N stretching band at 2270 cm^{-1} (2a) and 2255 cm^{-1} (2b) was accompanied by the appearance of a new, sharp band respectively at 3400 cm^{-1} and 3420 cm^{-1}, attributable to a primary amine or amide. The C=O stretching band of the ester underwent a distinct shift to lower frequencies, from 1740 cm^{-1} to 1677 cm^{-1} (2a) and 1670 cm^{-1} (2b).

In the ^1H NMR spectra it was observed that two doublets coupled to each other, one of the proton at the central carbon atom C(4) resonating at 5.56 ppm (2a) or 5.52 ppm (2b) and the other of the proton at the N(7) amide function, showing up at 7.16 ppm (2a) or 6.58 ppm (2b), were replaced after the reaction with 1 by a broad, exchangeable with D_2O, two proton signals at 6.17 (3a) or 6.20 (3b) ppm. In line with that, the ^{13}C NMR showed that after the reaction with 1 carbon C(4) became quaternary and substantially changed the environment which made it resonate at 158.92 ppm (3a) and 159.60 ppm (3b) in place of the original 41.82 ppm (2a) and 42.89 ppm (2b).

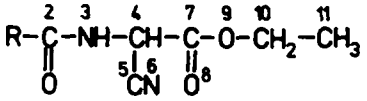
The ^{13}C NMR excluded the C=O to C=S exchange at the amide function, which according to literature[4,5] should result in about 30 ppm downfield shift of the signal. Instead of that the absorption of the carbon deriving from the amide carbonyl underwent an upfield shift of 27.74 ppm (2a→3a) and 21.99 ppm (2b→3b), to the region of heteroaromatic C=N.

The above data were consistent with the aminothiazole structures 3a and 3b, which have also been ascribed by Sen et al.[11,12] to the compounds having identical melting points, obtained in

the reaction of ethyl N-(ethoxycarbonylcyanomethyl) form-and acetimidate respectively, with H_2S in pyridine. Nevertheless, they were not completely definite for distinguishing the aminothiazoles from the other possible isomeric products 4. The latter compounds could have been expected to form if the thiazole ring closure was effected by incorporation not of the cyano group carbon, but of the ester carbonyl. This very reaction course was reported by Lawesson et al.[10], who obtained 2--phenyl-5-ethoxythiazole from 1-(N-benzoyl-glycyl)-ethyl ester subjected to 1 in refluxing xylene. The unambiguous confirmation of structure 3 was gained from an X-ray crystallographic investigation of 3a (vide infra).

Table 3

^1H and ^{13}C NMR data for 2 and 3 (δ, rel. to internal TMS, $CDCl_3$)[a]



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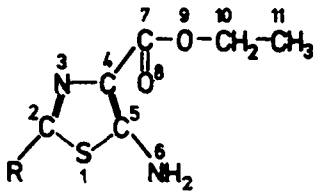

3

a R = H
b R = CH_3
c R = C_6H_5

	H at:	C(11)	C(10)	C(4)	N(6)	N(3)	C(2)	C(2)-CH_3	Benzene ring
2a		1.37 t[b],3H	4.37 q,2H	5.55 d,1H	- -	7.16 d,1H,b,ex	8.30 s,1H	-	-
2b		1.37 t,3H	4.36 q,2H	5.52 d,1H	-	6.58 d,1H,b,ex	-	2,12 s,3H	-
2c		1.36 t,3H	4.36 q,2H	5.72 d,1H	- -	-	-	-	7.31-7.89 m,5H
3a		1.41 t,3H	4.39 q,2H	-	6.17 s,2H,b,ex	-	7.86 s,1H	-	-
3b		1.39 t,3H	4.37 q,2H	-	6.20 s,2H,b,ex	-	-	2.51 s,3H	-
3c		1.42 t,3H	4.41 q,2H	-	6.31 s,2H,b,ex	-	-	-	7.31-7.82 m,5H

	C(11)	C(10)	C(4)	C(5)	C(7)	C(2)	C(2)-CH_3	Benzene ring
2a	13.68 Q[b]	64.14 T	41.82 D	113.68 S	162.14 S	162.84 D	-	-
2b	13.97 Q	64.30 T	42.89 D	113.97 S	163.45 S	169.65 S	22.58 Q	-
2c	13.92 Qt	64.20 Tq	43.72 D	114.26 Sd	163.68 Snc	167.15 Snc	-	127.54 128.84 132.14 132.69
3a	14.40 Q	60.49 T	158.92 S	122.50 S	164.53 S	135.10 D	-	
3b	14.55 Q	60.38 T	159.60 S	120.60 S	164.50 S	147.65 S	19.04 Q	-
3c	14.57 Qt	60.63 Tq	159.83 Ss	122.72 Snc	164.81 St	149.43 St	-	126.13 128.79 128.38 133.39

[a] Numbering of the atoms is according to the one used in the X-ray analysis.

[b] Capital letters refer to the patterns resulting from directly bonded ^{13}C-^1H couplings, lower case letters to those from ^{13}C-^1H couplings over more than one bond and ^1H-^1H couplings. S or s, singlet; D or d, doublet; T or t, triplet; Q or q, quartet; m, multiplet; b, broad; ex, exchangeable with D_2O; nc splittings not clear.

To check the possible influence of the benzoyl substituent and the reaction temperature on the direction of the ring closure we performed the reaction on 2-benzoylamino-2-cyanoacetic acid ethyl ester 2c at 80° and 110°C. Analogously to its 2-formyl and 2-acetyl congeners, 2c was transformed into 5-amino-2-phenylthiazole-4-carboxylic acid ethyl ester 3c, which demonstrated the same characteristic spectral features (Tables 1-3). No side reaction leading to a product of an alternative thiazole ring closure was observed. The low yield of 3c was caused by the fact that a total conversion of 2c could not be obtained regardless of the amount of 1 used. Similar observations were made earlier on some other reactions with this reagent[7].

The formation of an aminothiazole structure by involvement of the cyano group was also in contrast to the previously reported inertness of this group towards 1. The cyano substituent in 2,3--unsaturated esters stayed intact when these compounds were thiated even under more stringent conditions (refluxing xylene)[7].

The final outcome of the reactions of polyfunctional compounds with 2,4-bis(4-methoxyphenyl)--1,3,2,4-dithiadiphosphetane 2,4-disulfide seems therefore to be strongly influenced by the character of different functionalities and the competition between them.

X-RAY STRUCTURE DETERMINATION

Crystals are monoclinic, P $2_1/n$, with a = 9.1239(8), b = 11.903(1), c = 7.4043(5)Å, β = 94.04(6)°, V = 802.13Å^3, D_x = 1.43 gcm^{-3} for Z=4. X-Ray diffraction data were collected on a Syntex $P2_1$ diffractometer from a crystal with dimensions 0.25 x 0.35 x 0.40 mm. Graphite monochromatized copper radiation (1.54178 Å) was used and 1259 unique reflections were measured of which 1201 had $I \geq 1.96\sigma/I/$ and were considered observed. The structure was solved by direct methods /H-atoms found in ΔF map/ and refined by least squares techniques with anisotropic thermal parameters for non-hydrogen atoms and isotropic B for hydrogen atoms. The final refinement included also an empirical isotropic extinction parameter x, used to correct the calculated structure factor. Final R = 0.048. Programs used: MULTAN 80[13], SHELX 76[14], local programs[15], PLUTO[16] and ORTEP[17].

Table 4

Fractional coordinates and equivalent isotropic thermal parameters.

Atom	X	Y	Z	UEQ
S(1)	0.21941(8)	0.17536(6)	0.3414(1)	0.0593(3)
C(2)	0.3602(3)	0.1526(2)	0.2017(4)	0.059(1)
N(3)	0.3658(2)	0.2211(2)	0.0671(3)	0.0517(8)
C(4)	0.2541(2)	0.2994(2)	0.0676(3)	0.0415(8)
C(5)	0.1607(2)	0.2879(2)	0.2066(3)	0.0425(8)
N(6)	0.0437(2)	0.3490(2)	0.2444(3)	0.0551(8)
C(7)	0.2355(2)	0.3864(2)	-0.0685(3)	0.0419(8)
O(8)	0.1441(2)	0.4602(1)	-0.0662(2)	0.0507(6)
O(9)	0.3270(2)	0.3741(2)	-0.2011(3)	0.0638(7)
C(10)	0.3160(4)	0.4576(3)	-0.3467(4)	0.068(1)
C(11)	0.4048(4)	0.5578(3)	-0.2970(5)	0.078(1)

Structure

Bond lengths and angles are given in Table 5[18]. The shape of the molecule with numbering system is shown in Fig. 1. The molecule consists of the thiazole ring, an amino group bonded to C(5) and an ethoxycarbonyl group joined to C(4).

Bond lengths /with the exception of elongated C(4)-C(5)/ and angles in the thiazole ring are comparable with the data for other thiazole derivatives[19,20,21]. The C(4)-C(7) exoxyclic bond is distinctly shortened (1.447(3) Å) what indicates the resonance interactions in the system. The thiazole ring is planar with N(6) and C(7) atoms lying in that plane. The carbonyl group is disposed syn to the amine N-atom, the torsion angle C(5)-C(4)-C(7)-O(8) equals to 4.9(3)°. An intramolecular hydrogen bond /O(8)...H(61) = 2.30(4), N(6)-H(61) = 0.84(4) Å and H-bond angle 124(2)°/ closes the six-membered ring. The torsion angle C(4)-C(7)-C(9)-C(10) of value 179.5(3)° shows the planarity of that fragment. The ethyl group is almost perpendicular to the rest of the molecule,

the C(7)-O(9)-C(10)-C(11) torsion angle equals to 85.0(3)°.

Table 5

Bond distances (Å) and angles (°).

S(1)-C(2)	1.726(3)	C(2)-S(1)-C(5)	89.4(1)
S(1)-C(5)	1.732(2)	S(1)-C(2)-N(3)	115.8(2)
C(2)-N(3)	1.292(4)	C(2)-N(3)-C(4)	110.8(3)
N(3)-C(4)	1.381(3)	N(3)-C(4)-C(5)	115.3(2)
C(4)-C(5)	1.389(3)	C(4)-C(5)-S(1)	108.8(2)
C(5)-N(6)	1.338(3)	C(4)-C(5)-N(6)	129.9(2)
C(4)-C(7)	1.447(3)	S(1)-C(5)-N(6)	121.3(2)
C(7)-O(8)	1.213(3)	N(3)-C(4)-C(7)	122.1(2)
C(7)-C(9)	1.341(3)	C(5)-C(4)-C(7)	122.6(2)
C(9)-C(10)	1.465(4)	C(4)-C(7)-O(8)	123.8(2)
C(10)-C(11)	1.473(5)	O(8)-C(7)-O(9)	123.6(2)
		C(7)-O(9)-C(10)	116.8(2)
		O(9)-C(10)-C(11)	111.0(3)

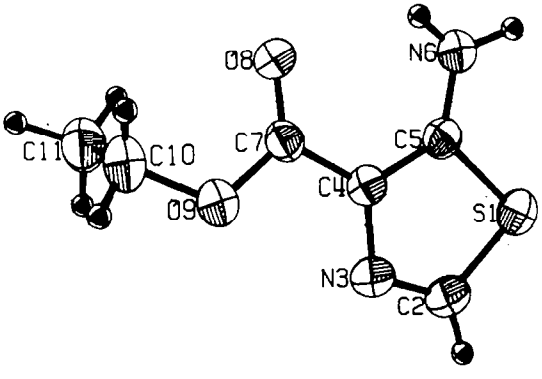

Fig. 1. View of the molecule showing the atomic numbering.

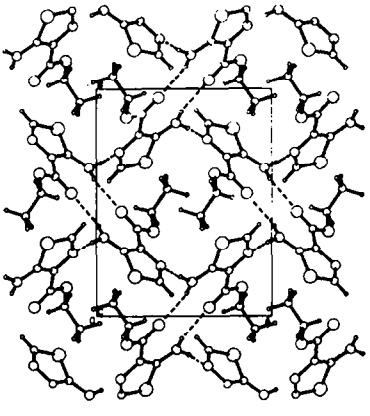

Fig. 2. Projection along c showing molecular packing and hydrogen bonding.

The molecule is involved in the intermolecular hydrogen bond network. The amine hydrogen atoms are donors /H(61) is involved in intra- and intermolecular bifurcated hydrogen bond/, the O(8) and N(3) are acceptors. Two N-H...O bonds form dimers around the symmetry center and this donors are joined by N-H...N(3) bonds into the three-dimensional network. The molecular packing and the hydrogen bond system is shown in Fig. 2.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Elemental analyses were performed on a Hewlett Packard 185 and a Perkin-Elmer 240 CHN analysers. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX 900 FT NMR spectrometer in $CDCl_3$ solutions. The chemical shifts are reported in parts per million on the δ scale, referenced to internal TMS. IR spectra were determined on a Perkin-Elmer Model 180 instrument in KBr pellets. Mass spectra were recorded at 75 eV on a JEOL JMS-D-100 spectrometer. Analytical TLC was performed on Merck precoated silica gel F_{254} plates using chloroform-methanol 9:1 as a solvent. For a preparative short column chromatography Merck TLC silica gel type 60H was used.

Compound 1 was prepared according to[5], compound 2a as described earlier[22], 2b and 2c, analogously to 2a.

2c mp. 133-34°C. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.09; H, 5.17; N, 12.07. Found: C, 62.13; H,

5.06; N, 12.28. Spectroscopic data in the Tables 2 and 3.

General procedure for the synthesis of 5-amino-2-R-thiazole-4-carboxylic acids ethyl esters 3a,b,c. In a typical experiment 2-acylamino-2-cyanoacetic acid ethyl ester 2a,b,c (10 mmoles) was dissolved in anhydrous benzene (25 mL), then 1 (5 mmoles) was added and the mixture was refluxed for 24 h with an exclusion of moisture. TLC showed two distinct spots and some minor contaminations. Solvent was removed in vacuo, the residue was dissolved in a small volume of ethanol, dispersed on silica gel by coevaporation and applied on a silica gel short column / ϕ 5.5 cm, 100 g of adsorbent/. It was eluted with chloroform-anhydrous ethanol 95:5 solvent mixture. The introductory spectral data indicated in the compound of higher Rf value the incorporation of p-methoxy phenyl structural unit of the reagent 1. The fraction showing the lower Rf value was collected and recrystallized from benzene to give thiazole derivatives 3a,b,c. In case of compound 3c the purification over preparative TLC /Merck silica gel 60 F_{254} layer thickness 2 mm/, solvent chloroform-anhydrous ethanol (50:1) gave better results than short column chromatography. Melting points, yields, microanalytical and spectroscopic data are given in Tables 1-3.

ACKNOWLEDGEMENT

This work was partly supported by the Polish Academy of Sciences Project MR-I.12.1.7.7. We thank Ms. Z. Gdaniec, Mr. M. Popenda and Ms. E. Pasternak for recording the NMR spectra.

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