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SYNTHESIS OF [(THIAZOL-2-YLAMINO)-METHYLENE]BISPHOSPHONIC ACIDS

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A method for the synthesis of [(thiazol-2-ylamino)methylene]bisphosphonic acids from (aminomethylene)-bisphosphonic acid through 3-N-unsubstituted (thioureidomethylene)bisphosphonic acid was proposed.

Keywords: bisphosphonate, thiazole, cyclization.

Among bisphosphonate derivatives containing heterocycles biologically active compounds are found [1-3]. We have synthesized a series of 3-substituted (thiazol-2-ylaminomethylene)bisphosphonates [4, 5] with phytotoxic activity by the condensation of (thioureidomethylene)bisphosphonic acids with halo ketones. Biological activity has also been found for tetraesters of [(thiazol-2-yl)aminomethylene]bisphosphonic acids unsubstituted at the position N-3 synthesized by the condensation of aminothiazoles with triethyl orthoformate [7].

In the present work, we attempted to extend our method for the Hantzsch condensation to the synthesis of [(thiazolylamino)methylene]bisphosphonic acids unsubstituted at position N-3. (Thioureidomethylene)bisphosphonic acid **1** required for this reaction was synthesized by the acid-catalyzed decomposition of [(*tert*-butylthioureido)methylene]bisphosphonic acid **2**, which we obtained previously as the disodium salt from (aminomethylene)bisphosphonic acid **3** [8]. Since acid **2** is unstable in the free state, it was used *in situ* without separation from the reaction mixture. Acid **2** decomposes in hydrochloric acid with loss of the *tert*-butyl residue to give (thioureidomethylene)bisphosphonic acid **1**. This reaction proceeds under milder conditions than the decomposition described for *tert*-butylthiourea [9], which was carried out by heating in concentrated hydrochloric acid at reflux. However, the decomposition of acid **2** proceeds with formation of (aminomethylene)bisphosphonic acid **3** as a side product. The optimal conditions for the formation of desired acid **1** according to the ^{31}P NMR spectrum of the reaction mixture are obtained using 10% hydrochloric acid at 90°C. Under these conditions, the decomposition of acid **2** requires 10 min and leads to a mixture consisting of 83% of the desired acid **1** and 17% of the by-product acid **3**. An attempt to use concentrated hydrochloric acid led to a mixture of not readily identifiable side products. Acid **1** precipitated from the mixture as fine-crystalline mono-(triethylammonium) salt **4**, which is stable and can be stored under ordinary conditions without decomposition.

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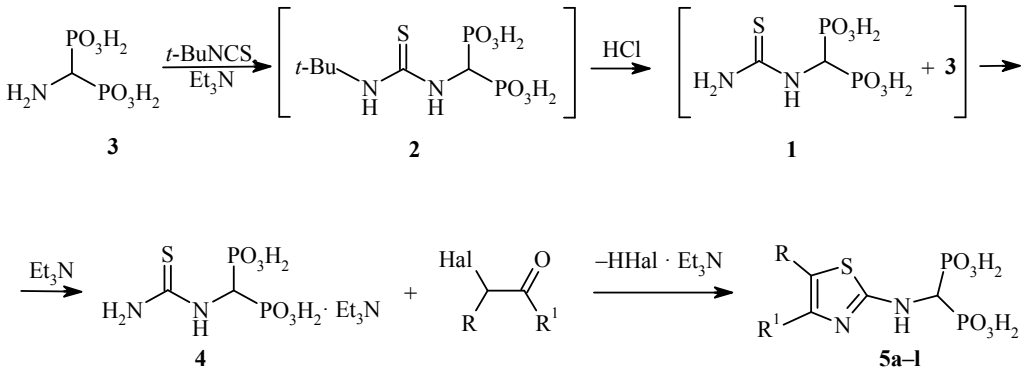

a–j R = H, **a** R^1 = Me, **b** R^1 = Et, **c** R^1 = COOH, **d** R^1 = CH_2COOMe, **e** R^1 = Ph, **f** R^1 = 4-ClC_6H_4, **g** R^1 = 4-MeC_6H_4, **h** R^1 = 3,4-$(HO)_2C_6H_3$, **i** R^1 = 2,4-$Cl_2C_6H_3$, **j** R^1 = β-naphthyl; **k** R = R^1 = Me; **l** R = COOMe, R^1 = Me; Hal = Br or Cl

The ^{1}H NMR spectra of salt **4** show two sets of signals corresponding to two isomers (21 and 79% in DMSO-d_6). Such *(E)-(Z)* isomerism related to the hindered rotation about the C(S)–N bonds due to their partial double bond character is described in our previous work for (N-3)-substituted analogs of compound **4** [5].

TABLE 1. Characteristics of Products **4** and **5a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
4	$C_2H_8N_2O_6P_2S\cdot C_6H_{15}N$	27.18 / 27.35	6.68 / 6.60	11.8 / 12.0	120	51
5a	$C_5H_{10}N_2O_6P_2S$	20.65 / 20.84	3.45 / 3.50	9.58 / 9.72	>215	40
5b	$C_6H_{12}N_2O_6P_2S$	23.54 / 23.85	4.29 / 4.00	8.81 / 9.27	>190	79
5c	$C_5H_8N_2O_8P_2S$	19.19 / 18.88	2.86 / 2.53	8.55 / 8.81	>246	75
5d	$C_7H_{12}N_2O_8P_2S$	24.46 / 24.29	3.59 / 3.49	8.14 / 8.09	>245	63
5e	$C_{10}H_{12}N_2O_6P_2S$	34.50 / 34.30	3.58 / 3.45	8.16 / 8.00	>260	96
5f	$C_{10}H_{11}ClN_2O_6P_2S$	30.98 / 31.22	3.15 / 2.88	6.99 / 7.28	>260	69
5g	$C_{11}H_{14}N_2O_6P_2S$	36.60 / 36.27	3.68 / 3.87	7.80 / 7.69	>240	68
5h	$C_{10}H_{12}N_2O_8P_2S$	31.18 / 31.42	3.32 / 3.16	7.12 / 7.33	>210	40
5i	$C_{10}H_{10}Cl_2N_2O_6P_2S$	28.55 / 28.66	2.59 / 2.40	6.73 / 6.68	>265	54
5j	$C_{14}H_{14}N_2O_6P_2S$	41.70 / 42.01	3.77 / 3.53	7.15 / 7.00	>225	62
5k	$C_6H_{12}N_2O_6P_2S$	23.45 / 23.75	4.06 / 4.00	9.49 / 9.27	>223	79
5l	$C_7H_{12}N_2O_8P_2S$	24.22 / 24.29	3.62 / 3.49	8.06 / 8.09	>200	58

* All obtained compounds decompose upon melting.

TABLE 2. ^{1}H NMR Spectra of [(Thiazol-2-ylamino)methylene]bisphosphonic Acids **5a-l**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*	
	C<u>H</u>$(PO_3H_2)_2$ (1H, t)	R, R[1]
5a	3.83 (*J* = 17.9)	2.03 (3H, s, CH_3); 6.04 (1H, s, H-5 thiazole)
5b	4.64 (*J* = 21.5)	1.15 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 3.05 (2H, m, *J* = 7.2, $C\underline{H}_2CH_3$); 7.45 (1H, s, H-5 thiazole)
5c	3.98 (*J* = 18.0)	6.94 (1H, s, H-5 thiazole)
5d	3.71 (*J* = 18.9)	3.43 (2H, s, CH_2); 3.60 (3H, s, CH_3); 6.24 (1H, s, H-5 thiazole)
5e	4.24 (*J* = 18.9)	7.20–7.83 (5H, m, H Ar); 6.97 (1H, s, H-5 thiazole)
5f	4.79 (*J* = 21.5)	7.13 (1H, s, H-5 thiazole); 7.44 (2H, d, *J* = 8.2, H Ar); 7.85 (2H, d, *J* = 8.2, H Ar)
5g	4.69 (*J* = 21.2)	2.31 (3H, s, CH_3); 7.00 (1H, s, H-5 thiazole); 7.20 (2H, d, *J* = 8.2, H Ar); 7.70 (2H, d, *J* = 8.2, H Ar)
5h	4.06 (br.)	6.56 (1H, s, H-5 thiazole); 6.66 (1H, d, *J* = 8.0, H Ar); 7.02 (1H, dd, *J* = 8.0, *J* = 1.7, H Ar); 7.37 (1H, d, *J* = 1.7, H Ar)
5i	4.06 (*J* = 18.6)	7.09 (1H, s, H-5 thiazole); 7.46 (1H, d, *J* = 8.6, H Ar); 7.62 (1H, s, H Ar); 7.96 (1H, d, *J* = 8.6, H Ar)
5j	3.02 (*J* = 18.9)	6.78–7.59 (7H, m, H Ar); 6.32 (1H, s, H-5 thiazole)
5k	3.46 (*J* = 18.3)	1.87 (3H, s, CH_3); 2.02 (3H, s, CH_3)
5l[*2]	4.72 (br.)	2.41 (3H, s, CH_3); 4.72 (3H, c, CH_3)
5l	4.14 (br.)	2.33 (3H, s, CH_3); 4.14 (3H, s, OCH_3)

*The ^{1}H NMR spectra for compounds **5a,c-e,h,i,k,l** were taken in DMSO-d_6 + 2.5% Et_3N, the spectra for compounds **5b,f,g** were taken in DMSO-d_6, and the spectrum for **5j** was taken in D_2O + Na_2CO_3 (added until dissolution).
*[2]The ^{1}H NMR spectrum was taken in DMSO-d_6.

Salt **4** readily reacts with halo ketones in ethanolic solution to give rapidly crystallizing [(thiazol-2-ylamino)methylene]bisphosphonic acids **5a-l**.

Acids **5** are colorless, high-melting compounds, which decompose upon heating, have low solubility in DMSO, and are virtually insoluble in water, acetone, and alcohols. On the other hand, these acids readily dissolve in water in the presence of various bases or in DMSO with added triethylamine to give salts.

Thus, we have developed a method for the synthesis of (thioureidomethylene)bisphosphonic acid unsubstituted at position N-3 and for the conversion of this compound into [(thiazol-2-ylamino)-methylene]bisphosphonic acid.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian VXR-300 spectrometer at 300 MHz with TMS as internal standard for the DMSO-d_6 solutions. The chemical shifts for the solutions in D_2O are given relative to TMS as external standard.

Triethylammonium Salt of (Thioureidomethylene)bisphosphonic Acid (4) [8]. *t*-BuNCS (3 ml, 25 mmol) was added to a solution of (aminomethylene)bisphosphonic acid (**3**) (3.82 g, 20 mmol) in a mixture of methanol (50 ml), water (10 ml), and triethylamine (15 ml, 108 mmol) and left for 24 h at 60°C (heating the mixture to reflux leads to decomposition of the product). The mixture was evaporated under reduced pressure at

30°C to give a thick residue, which was dissolved in 60 ml water. The side products were extracted with ether (3×20 ml) and the solution was decolorized using activated carbon. Concentrated hydrochloric acid (10 ml) was added to the aqueous phase and heated for 10 min at 90°C. The mixture was evaporated in vacuum at 30°C to leave a thick residue, which was dissolved in 30 ml 2-propanol and left to crystallize for one week at 0°C. The colorless precipitate was filtered off and washed with 2-propanol. Salt **4**, which readily dissolves in water, was dried in vacuum at 30°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.17 (9H, t, *J* = 7.3, $3CH_2C\underline{H}_3$); 3.06 (6H, q, *J* = 7.3, $3C\underline{H}_2CH_3$); 3.99 (0.21H, td, $^2J_{P–H}$ = 18.8, ^3J = 8.4) and 5.07 (0.79H, td, $^2J_{P–H}$ = 20.5, ^3J = 9.8, CH); 6.14 (0.21H, m) and 8.84 (0.79H, m, NH); 7.32 (1H, br. s, NH); 9.94 (1H, s, NH).

[(Thiazol-2-ylamino)methylene]bisphosphonic Acids 5a-l (General Method). Corresponding chloro (for compounds **5c,d,h,i,k,l**) or bromo ketone (6-7 mmol) was added to a solution of compound **4** (1.76 g, 5 mmol) in methanol (10 ml) and heated under reflux for 10 min. The reaction mixture was cooled and 1 ml concentrated hydrobromic acid was added. The mixture was left at 0°C for 12 h for crystallization. The precipitate was filtered off, washed with methanol, and dried in the air.

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