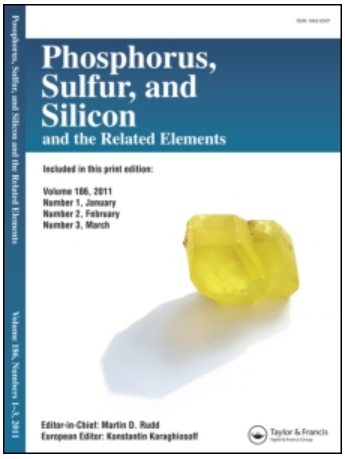

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A Convenient Synthesis of ω-(2-Aryl-4-oxothiazolidin-3-Yl)alkylphosphonic Acids via In Situ-Generated Arylideneaminoalkylphosphonic Acids

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A CONVENIENT SYNTHESIS OF ω-(2-ARYL-4-OXOTHIAZOLIDIN-3-YL)ALKYLPHOSPHONIC ACIDS VIA IN SITU–GENERATED ARYLIDENEAMINOALKYLPHOSPHONIC ACIDS

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***ω*-(2-Aryl-4-oxothiazolidin-3-yl)alkylphosphonic acids are prepared in an easy workup procedure by the addition of methyl mercaptoacetate to in situ–generated arylideneaminoalkyl phosphonic acids.**

Keywords Aminophosphonic acids; arylideneaminophosphonic acids; cyclizations; 4-thiazolidinones

INTRODUCTION

4-Thiazolidinones constitute a class of compounds that exhibit very useful properties and utilities. For instance, they have been demonstrated to possess a broad spectrum of biological activities such as antitumor,[1] antibacterial,[2] antifungal,[2] antitubercular,[3] anti-HIV-RT,[4] antiinflammatory,[5] and many others.[6] It has been shown that the presence of a phosphonyl group could influence the biological functions of heterocyclic systems.[7] Some synthetic approaches to 4-thiazolidinones bearing a dialkylphosphonic ester moiety have already been reported. One of the methods requires the reaction of 5-arylidene-2-thioxo-4-thiazolidinones with phosphonoacetates and leads to the fused-thiazole derivatives.[8] Another method is based on the reaction of imidoyl phosphonates with mercaptoacetic acid or its alkyl esters.[9,10] The phosphonyl functionalized 4-thiazolidinones can also be prepared by the reaction of phosphonylated Schiff bases generated from aromatic aldehydes, aminophosphonic acid esters, and mercaptoacetic acid;[11] however all these methods lead to phosphonic esters.

In this article, we provide a new, one-pot approach to *ω*-(2-aryl-4-oxothiazolidin-3-yl)alkylphosphonic acids.

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This work is dedicated to my mentor, Prof. Romuald Bartnik, University of Łódź, Łódź, Poland, on the occasion of his 70th birthday.
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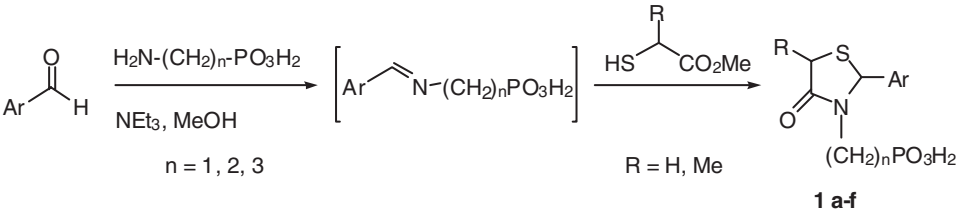
RESULTS AND DISCUSSION

Previously we have established an efficient route to N-benzyl functionalized aminoalkylphosphonic acids and ω-[(arylphosphonomethyl)amino]alkylphosphonic acids via in situ–generated arylideneaminoalkylphosphonic acids.[12,13] Now we have used these reactive arylideneaminoalkylphosphonic acids in the synthesis of 4-thiazolidinones bearing a phosphonic acid function. As shown in Scheme 1, the reaction requires two steps. First,

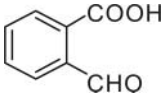
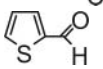
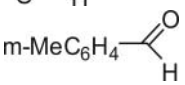
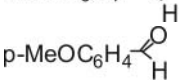
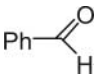
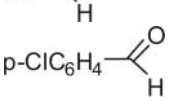


Scheme 1

we have generated the imine from the aminoalkylphosphonic acid (1 eq.) in methanol as solvent and in the presence of triethylamine (3 eq.). This stage required 1–2 h. Then, methyl mercaptoacetate was added, and the mixture was stirred for a period of 12–48 h. The resulting thiazolidinonephosphonic acids **1a–c** were isolated after a simple workup (Table I).

Similarly, thiazolidinonephosphonic acids **1d–f** (diastereoisomers mixtures) were prepared from methyl 2-mercaptopropionate; however, the trials with methyl 2-mercapto-2-methylpropionate failed, and the starting aminoacids were recovered. The same failure result was observed when we used methyl mercaptoacetate and 1-amino-1-methylethylphosphonic acid or 1-aminocyclohexylphosphonic acid as a substrate. Thus, it

Table I Synthesis of ω-(2-aryl-4-oxothiazolidin-3-yl)alkylphosphonic acids **1a–f**

Entry	Ar–CHO	$-(CH_2)_n-$	R	Imine formation conditions	Addition conditions	Product	Isolated yield (%)	Mp (°C)
a		$-CH_2-$	H	rt, 1 h	rt, 12 h	**1a**	50	191–194
b		$-(CH_2)_2-$	H	rt, 3 h	rt, 24 h	**1b**	41	178–181
c		$-(CH_2)_3-$	H	50°C, 1.5 h	50°C, 1.5 h/rt, 12 h	**1c**	73	137–139
d		$-CH_2-$	CH_3	rt, 1 h	rt, 48 h	**1d**	61	182–187
e		$-(CH_2)_2-$	CH_3	rt, 1h	rt, 12 h	**1e**	49	172–175
f		$-(CH_2)_3-$	CH_3	50°C, 1h	50°C, 4 h/rt, 12 h	**1f**	67	136–141

is probably that the steric hindrance both in the mercaptoester and in the aminophosphonic acid limits the scope of the method.

The final 4-thiazolidine phosphonic acids are stable compounds and can be stored at room temperature for months without decomposition. Their structure was confirmed by IR, NMR, and elemental or HRMS analysis.

In summary, the protocol described in this article provides a new and simple access to ω-(2-aryl-4-oxothiazolidin-3-yl)alkylphosphonic acids directly from easily available aminophosphonic acids, aromatic aldehydes, and mercaptoacetic esters. The reaction gives moderate to good yields and avoids a hydrolysis step, which is necessary during the preparation of such class of compounds.[14]

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained with a Bruker Avance III 600, a Varian Gemini 200, and a Tesla BS 687 spectrometer operating at 200 and 80 MHz, respectively, for ^{1}H (TMS); at 151, 50, and 20 MHz for ^{13}C; and at 243 and 80 MHz for ^{31}P (H_3PO_4). IR spectra were measured on a Specord 75 instrument and are reported in cm^{-1}. HRMS (EI, 70 eV) spectra were recorded on a Finnigan MAT 95 instrument. The elemental analyses were performed by the Laboratory of Microanalysis of the Centre of Molecular and Macromolecular Studies, Polish Academy of Science in Łódź.

ω-(2-Aryl-4-oxothiazolidin-3-yl)alkylphosphonic Acids 1a–f: General Procedure

To a suspension of primary aminophosphonic acid (10 mmol) in MeOH (100 mL), NEt_3 (3.00 g, 30 mmol, Table I, entries b–f; 4.00 g, 40 mmol, entry a) was added, and the mixture was stirred at rt for 20 min. Next, the aromatic aldehyde (10 mmol) was added, and stirring was continued (temperature and time given in Table I). To the clear solution thus obtained, methyl mecaptoacetate (1.06 g, 10 mmol, entries a–c) or methyl 2-mercaptopropionate (1.20 g, 10 mmol, entries d–f) was added, and stirring was continued (temperature and time given in Table I). Then the solvent was evaporated, and the residue was washed with Et_2O (3 × 50 mL, entries a–c, e, f). The residue thus obtained was worked up in different ways:

2-(4-Oxo-3-phosphonomethylthiazolidin-2-yl)benzoic Acid (1a)

The residue was dissolved in water (30 mL) and acidified with HCl (aq) solution (4 mol/dm^3, 8.5 mL). The product precipitated as colorless crystals. ^{1}H NMR (D_2O/NaOD, 200 MHz): $\delta = 2.77$ (dd, $^{2}J_{HA\text{-}HM} = 15.4$ Hz, $^{2}J_{PH} = 9.5$ Hz, 1H, PCH_AH_M), 3.63 (dAB, $^{2}J_{HA\text{-}HB} = 15.9$ Hz, $^{5}J_{PH} = 2.4$ Hz, 1H, SCH_AH_B), 3.74 (AB, $^{2}J_{HA\text{-}HB} = 15.9$ Hz, 1H, SCH_AH_B), 3.96 (dd, $^{2}J_{HA\text{-}HM} = 15.4$ Hz, $^{2}J_{PH} = 13.3$ Hz, 1H, PCH_AH_M), 6.47 (s, 1H, CH), 7.06–7.59 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 50 MHz): $\delta = 34.0$ (C-5), 45.1 (d, $^{1}J_{PC} = 137.5$ Hz, CH_2), 64.3 (C-2), 126.2 (CH_{arom}), 130.9 (CH_{arom}), 131.6 (CH_{arom}), 132.8 (CH_{arom}), 139.4 (Cq_{arom}), 140.4 (Cq_{arom}), 176.6 (d, $^{3}J_{PC} = 2.2$ Hz, C-4), 178.8 (COOH). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 12.9$. IR (KBr): 3397–2573 (OH), 1663 (C═O), 1279 (P═O), 1025 (P—O). Anal. Calcd for $C_{11}H_{12}NO_6PS \cdot H_2O$: C, 39.41; H, 4.21%. Found: C, 39.85; H, 4.39%.

2-[4-Oxo-2-(thiophen-2-yl)thiazolidin-3-yl]ethylphosphonic Acid (1b)

The residue was dissolved in water (30 mL), charcoal was added, and the mixture stirred at rt for 1 h. The mixture was filtered, and the filtrate was acidified with HCl (aq) solution (4 mol/dm^3, 6.3 mL). The product precipitated as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): δ = 1.28–2.24 (m, 2H, CH_2P), 2.94–4.12 (m, 4H, $CH_2N + CH_2S$), 6.30 (s, 1H, CH), 7.05–7.68 (m, 3H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 50 MHz): δ = 28.0 (d, $^1J_{PC}$ = 130.1 Hz, CH_2), 35.3 (C-5), 41.2 (CH_2N), 61.8 (C-2), 129.8 (CH_{arom}), 130.7 (CH_{arom}), 131.0 (CH_{arom}), 145.6 (Cq_{arom}), 174.9 (C-4). ^{31}P NMR (D_2O/NaOD, 80 MHz): δ = 16.6. IR (KBr): 3425–2273 (OH), 1640 (C═O), 1198 (P═O), 1000 (P—O). HRMS (EI) Calcd for $C_9H_{12}NO_4PS_2$: 292.9945. Found: 292.9947.

3-[4-Oxo-2-(3-tolyl)thiazolidin-3-yl]propylphosphonic Acid (1c)

The residue was dissolved in MeOH (5 mL) and NaOMe/MeOH solution (1 mol/dm^3, 24 mL) was added. Then the solvent was evaporated. The residue was dissolved in water (30 mL), acidified with HCl (aq) solution (4 mol/dm^3, 6.3 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was evaporated and the residue was crystallized from water to give the product as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): δ = 1.04–1.97 (m, 4H, $2CH_2$), 2.29 (s, 3H, CH_3), 2.47–2.92 (m, 1H, CH_2N), 3.42–3.90 (m, 3H, $CH_2N + CH_2S$), 5.93 (s, 1H, CH), 7.11–7.45 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 20 MHz): δ = 22.0 (CH_3), 22.9 (d, $^2J_{PC}$ = 3.7 Hz, CH_2), 27.7 (d, $^1J_{PC}$ = 130.7 Hz, CH_2), 34.2 (C-5), 45.8 (d,$^3J_{PC}$ = 20.7 Hz, CH_2), 65.1 (C-2), 125.7 (CH_{arom}), 129.1 (CH_{arom}), 130.7 (CH_{arom}), 131.6 (CH_{arom}), 140.8 (Cq_{arom}), 141.0 (Cq_{arom}), 175.5 (C-4). ^{31}P NMR (D_2O/NaOD, 80 MHz): δ = 19.9. IR (KBr): 3431–2287 (OH), 1647 (C═O), 1179 (P═O), 1006 (P—O). HRMS (EI) Calcd for $C_{13}H_{18}NO_4PS$: 315.0694. Found: 315.0695.

[2-(4-Methoxyphenyl)-5-methyl-4-oxothiazolidin-3-yl]methylphosphonic Acid (1d)

The residue was mixed with HCl (aq) solution (1 mol/dm^3, 28 mL) and the resulting precipitate washed with acetone/Et_2O (1/4, 5 mL) to give the product as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): δ = 1.46 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 2.56 (dd, $^2J_{HA\text{-}HM}$ = 15.1 Hz, $^2J_{PH}$ = 9.3 Hz, 1H, PCH_AH_M), 3.67–3.81 (m, 3H, OCH_3 + 1H, PCH_AH_M), 4.05 (dq, $^3J_{HH}$ = 6.9 Hz, $^5J_{PH}$ = 2.2 Hz, 1H, CHCO), 6.09 (s, 1H, CHN), 6.87–7.22 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 151 MHz): δ = 18.8 (CH_3, minor), 20.0 (CH_3, major), 41.3 (C-5, minor), 41.4 (d, $^1J_{PC}$ = 147.9 Hz, CH_2P, minor), 41.5 (d, $^1J_{PC}$ = 141.9 Hz, CH_2P, major), 42.2 (C-5, major), 5.6 (OCH_3, major + minor), 61.5 (C-2, minor), 61.7 (C-2, major), 114.7 (CH_{arom}, major + minor), 128.3 (CH_{arom}, minor), 128.8 (CH_{arom}, major), 131.5 (Cq_{arom}, major), 131.8 (Cq_{arom}, minor), 159.5 (Cq_{arom}, major + minor), 175.5 (d, $^3J_{PC}$ = 1.5 Hz, C-4, major), 175.6 (d, $^3J_{PC}$ = 1.5 Hz, C-4, minor). ^{31}P NMR (D_2O/NaOD, 243 MHz): δ = 13.2, 13.1 (93:7). IR (KBr): 3423–2325 (OH), 1660 (C═O), 1253 (P═O), 1012 (P—O). HRMS (EI) Calcd for $C_{12}H_{16}NO_5PS$: 317.0487. Found: 317.0497.

2-(5-Methyl-4-oxo-2-phenylthiazolidin-3-yl)ethylphosphonic Acid (1e)

The residue was dissolved in MeOH (5 mL) and NaOMe/MeOH solution (1 mol/dm^3, 24 mL) was added. Then the solvent was evaporated. The residue was dissolved in MeOH (30 mL), acidified with HCl/MeOH (4 mol/dm^3, 6.4 mL) and evaporated. The residue thus

obtained was dissolved in EtOH (20 mL) and filtered. The filtrate was evaporated, and the residue was crystallized from ethyl acetate. The product was obtained as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): $\delta = 1.22–2.08$ (m, 5H, $CH_3 + CH_2P$), 2.81–3.26 (m, 1H, CH_2P), 3.57–4.33 (m, 2H, $CH_2P + CHCO$), 5.97 (s, 1H, CHN), 7.51 (s, 5H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 50 MHz): $\delta = 21.2$ (CH_3, minor), 22.3 (CH_3, major), 29.1 (d, $^1J_{PC} = 124.5$ Hz, CH_2P, major), 29.4 (d, $^1J_{PC} = 124.5$ Hz, CH_2P, minor), 42.9 (CH_2N, minor + major), 44.2 (C-5, minor), 45.0 (C-5, major), 64.0 (C-2, minor), 64.4 (C-2, major), 129.4 (CH_{arom}, minor), 129.9 (CH_{arom}, major), 131.7 (CH_{arom}, major), 131.8 (CH_{arom}, major + minor), 141.3 (Cq_{arom}, major), 141.8 (Cq_{arom}, minor), 178.6 (C-4, major + minor). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 15.71, 15.74$ (1:2). IR (KBr): 3439–2303 (OH), 1679 (C═O), 1255 (P═O), 1000 (P—O). HRMS (EI) Calcd for $C_{12}H_{16}NO_4PS$: 301.0538. Found: 301.0537.

3-[2-(4-Chlorophenyl)-5-methyl-4-oxothiazolidin-3-yl]propylphosphonic Acid (1f)

The residue was dissolved in MeOH (5 mL), and NaOMe/MeOH solution (1 mol/dm^3, 24 mL) was added. Then the solvent was evaporated. The residue was acidified with HCl (aq) solution (4 mol/dm^3, 6.3 mL) and the product was obtained as colorless crystals. ^{1}H NMR (D_2O/NaOD, 80 MHz): $\delta = 1.16–1.88$ (m, 7H, $CH_3 + CH_2CH_2P$), 2.60–2.92 (m, 1H, CH_2P), 3.48–3.84 (m, 1H, CH_2P), 4.12 (q, $^3J_{HH} = 7.1$ Hz, 1H, CHCO), 5.91 (s, 1H, CHN), 7.25–7.90 (m, 4H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 50 MHz): $\delta = 21.6$ (CH_3, minor), 22.2 (CH_3, major), 23.7 (CH2, major + minor), 28.6 (d, $^1J_{PC} = 130.7$ Hz, CH_2P, major + minor), 44.3 (C-5, minor), 44.8 (C-5, major), 46.8 (d, $^3J_{PC} = 20.8$ Hz, CH_2N, major + minor), 63.2 (C-2, minor), 63.5 (C-2, major), 130,9 ($2CH_{arom}$, minor), 131.6 ($2CH_{arom}$, major), 136.6 (Cq_{arom}, minor), 136.8 (Cq_{arom}, major), 139.7 (Cq_{arom}, major), 140.0 (Cq_{arom}, minor), 178.6 (C-4, minor + major). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 19.80, 19.82$ (1:3). IR (KBr): 3442–2343 (OH), 1637 (C═O), 1181 (P═O), 1015 (P—O). HRMS (EI) Calcd for $C_{13}H_{17}ClNO_4PS$: 349.0304. Found: 349.0289.

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