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A concise synthesis of protected diethyl 1-amino-2-hydroxyalkylphosphonates

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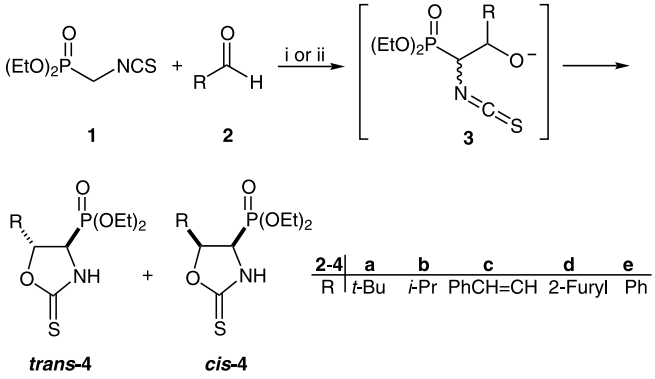
Abstract—An efficient diastereoselective synthesis of 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters from metallated diethyl isothiocyanomethylphosphonate and aldehydes has been developed. The three-step transformation of oxazolidine-2-thione derivatives into *N*-Boc 1-amino-2-hydroxyalkylphosphonic acid diethyl esters is also described.

Phosphonate analogues of α-amino acids have received considerable attention in bioorganic and medicinal chemistry due to their unique activities as peptidomimetics, such as transition state-analogue inhibitors and haptens of catalytic antibodies,[1] to name just a few. Although a variety of approaches to α-aminophosphonates have been developed,[1] the number of known 1-amino-2-hydroxyalkylphosphonic acid derivatives is limited, and only a few routes to aminophosphonates with two consecutive stereogenic centers (threonine analogues) have been reported. These methods include: (i) BINAP-Ru catalyzed hydrogenation of α-acetamido-β-ketophosphonic esters,[2] (ii) the reaction of benzenediazonium chloride with 2-oxoalkylphosphonates followed by reduction and hydrolysis,[2,3] (iii) azidation of derivatives of α,β-dihydroxyalkylphosphonic acid esters under Mitsunobu conditions followed by the reduction of the azide group thus formed,[4,6b] (iv) aldol reaction of metallated 1-isocyanoalkylphosphonic acid esters with aldehydes or ketones followed by the hydrolysis of the oxazolines thus formed,[5] (v) the synthesis of phosphothreonine via stereoselective addition of diethyl trimethylsilyl phosphite to *N*-silylated (*S*)-lacticimines,[6] oxidation of 1-amino-2-hydroxypropylphosphonous acid with $HgCl_2$,[7] the Michaelis–Arbuzov type reaction of *N*,*O*-acetals derived from L-threonine with trimethyl or triphenyl phosphite and $TiCl_4$,[8] or regioselective ammonolysis of phosphonomycin.[9]

On the other hand, organic isothiocyanates are a versatile class of heterocumulenes, which have found wide application in the construction of heterocyclic systems[10] and in the synthesis of β-hydroxy-α-amino acids or amino alcohols via oxazolidine-2-thiones.[11]

However, to the best of our knowledge this attractive methodology has not been applied to the synthesis of 1-amino-2-hydroxyalkylphosphonic acid derivatives. Our aim was to apply diethyl isothiocyanomethylphosphonate[12] **1**, a novel, easily available bifunctional isothiocyanate, in the synthesis of 5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters[13] **4**, which can be regarded as masked diethyl 1-amino-2-hydroxyalkylphosphonates.



Scheme 1. *Reagents and conditions*: (i) NaH (1.1 equiv.), THF, −5°C to rt, 1.5 h, followed by H_2O at rt; or (ii) *t*-BuOK (1.5 equiv.), THF, −40 to −20°C, 1.5 h, followed by H_2O at −20°C.

Keywords: oxazolidine-2-thiones; oxazolidin-2-one; diethyl 1-amino-2-hydroxyalkylphosphonates.

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We found that compound **1**, after metallation with sodium hydride or potassium *tert*-butoxide in THF, easily underwent condensation with representative aldehydes **2** to give, via intermediate anion **3**, the racemic mixture of *trans* and *cis*-5-substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters **4**,[14] according to Scheme 1. Reaction is limited to aromatic and some aliphatic aldehydes and adducts **4** can be separated by flash chromatography into single *trans*- and *cis*-isomers.

The results given in Table 1 clearly indicate that adducts **4** were all formed in good to excellent yields (70–95%) but, in principle, with low diastereoselecivity. Sterically hindered pivaldehyde is the exception, for which, independently of the base and temperature used, high *trans*-diastereoselectivity was observed (entries 1 and 2). Diastereoselectivity was slightly improved when potassium *tert*-butoxide at low temperature (below–20°C) was used for metallation (entries 2, 4 and 10). Reverse diastereoselectivity was also observed in most cases under these conditions (entries 4, 6, 8 and 10). At this point, however, it is difficult to rationalize these differences.

The stereochemistry of the oxazolidine-2-thiones **4** were determined by NOE difference experiments as well as an examination of the vicinal coupling constant of the ring protons H-4 and H-5. For compound *cis*-**4e** irradiation of H-5 produced a 14.5% enhancement of the signal for H-4, indicating a *cis* relationship between those protons on the oxazolidine-2-thione ring. For compound *trans*-**4e**, irradiation of H-5 showed a 6.8% enhancement of the signal for H-4.[15]

Additionally, the coupling constant J_{4-5} for **4e** (*trans*) was 6.5 Hz and the coupling constant J_{4-5} for **4e** (*cis*) was 9.5 Hz. This is consistent with the observation that *trans*-oxazolidin-2-ones as well as *trans*-oxazolidine-2-thiones have smaller coupling constants than the corresponding *cis*-diastereomers.[11a,16] The stereochemistry of the remaining compounds **4a–d** were determined by comparison of the coupling constants of the major and minor isomers.

Additionally, the phosphorus chemical shifts of **4** were consistent with a given diastereomer. In the ^{31}P NMR spectra of all oxazolidine-2-thiones **4** the signal of the *trans*-isomers appeared 0.5–1.5 ppm downfield relative to those of the *cis*-isomers (Table 1).

Having established the synthesis of oxazolidine-2-thiones **4**, we focused our attention on their transformation into *N*-Boc 1-amino-2-hydroxyalkylphosphonic acid diethyl esters **7** (Scheme 2).

Thus, the mixture of *trans*- and *cis*-adducts **4e**, selected as a representative substrate, was easily separated by crystallization from carbon tetrachloride (*cis*-**4e**) and flash chromatography (*trans*-**4e**) to give pure *trans*- and *cis*-**4e** in 40 and 42% yields, respectively.

By analogy with the literature procedure,[17] *N*-protection of *cis*-(5-phenyl-2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl ester **4e** was readily achieved with di-*tert*-butyldicarbonate in the presence of catalytic amounts of DMAP to give *cis*-**5e** in 96% yield. Subsequent oxidative desulfuration[17] of *cis*-**5e** by means of 30% hydrogen peroxide in formic acid provided a 95% yield of the desired *N*-Boc *cis*-(2-oxo-5-phenyloxazolidin-4-yl)phosphonic acid diethyl ester **6e**.

In the final step, *cis*-**6e** was found to undergo smooth ring opening to acyclic *anti*-(1-*tert*-butoxycarbonylamino-2-hydroxy-2-phenylethyl)phosphonic acid diethyl ester **7e** in 68% yield, upon treatment with Cs_2CO_3 (2 equiv.) in methanol–water (4:1).[18]

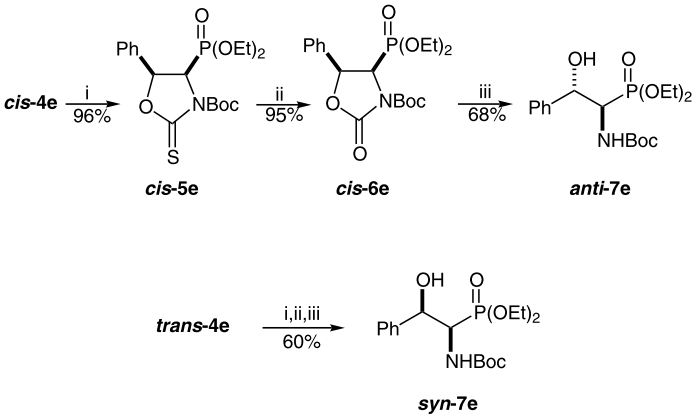
In the same sequence of reactions as above, *trans*-**4e** afforded *syn*-**7e**, exclusively in 60% overall yield.

In summary, we have demonstrated that the diastereoselective addition of diethyl isothiocyanomethylphosphonate **1** to representative aldehydes affords 1-amino-2-hydroxyalkylphosphonic acid diethyl esters **4** as fully protected, cyclic thiocarbamates. An efficient, three-step transformation of the adducts **4** into *N*-Boc 1-amino-2-hydroxyalkylphosphonic acid diethyl esters was also developed.

Table 1. 5-Substituted (2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl esters **4** prepared

Entry	Compd **4**	R	Base	Yield[a] (%)	*trans*:*cis*[b]	^{31}P NMR δ (ppm) *trans*/*cis*
1	**4a**	*t*-Bu	NaH	76	92:8	18.54/17.80
2			*t*-BuOK	70	100:0[c]	
3	**4b**	*i*-Pr	NaH	73	40:60	17.85/17.48
4			*t*-BuOK	95	80:20	
5	**4c**	PhCH=CH	NaH	84	41:59	17.00/16.50
6			*t*-BuOK	90	48:52	
7	**4d**	2-Furyl	NaH	81	41:59	16.45/14.95
8			*t*-BuOK	90	60:40	
9	**4e**	Ph	NaH	87	46:54	16.87/15.33
10			*t*-BuOK	86	72:28	

[a] Yield of isolated product.
[b] Diastereomer ratios measured by ^{31}P NMR.
[c] Only one diastereomer could be observed in the ^{31}P NMR spectrum of the crude product.



Scheme 2. *Reagents and conditions*: (i) Boc_2O (1.15 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, rt, 2 h; (ii) 30% H_2O_2 (28 equiv.), 98% HCO_2H, 0°C to rt, 1 h; (iii) Cs_2CO_3 (2 equiv.), MeOH–H_2O (4:1 v/v), rt, 3 h.

Work is now in progress to explore enantioselective versions of these transformations. Studies towards this goal and further applications of 1-(isothiocyano)alkylphosphonates in organic synthesis will be reported in due course.

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14. **General procedure for the synthesis of oxazolidine-2-thiones 4**:
    Method A: NaH (0.027 g, 1.1 equiv.) was added at −5°C to a solution of diethyl isothiocyanomethylphosphonate **1** (0.209 g, 1 mmol) in dry THF (10 mL). The mixture was stirred for 10 min at this temperature, followed by the addition of benzaldehyde (0.117 g, 1.1 mmol). After 1.5 h at rt, the reaction was quenched with water. Tetrahydrofuran was evaporated under reduced pressure and dichloromethane (40 mL) was added to the residue. The organic layer was separated and washed successively with water (5 mL), 5% aq. $KHSO_4$ (2×5 mL), water (2×5 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to give **4e** (0.275 g, 87%) as colorless crystals. The *cis*-isomer was isolated via crystallization from CCl_4 (7 mL) in 42% yield (mp = 170–172°C), and the *trans*-isomer was separated by flash chromatography on silica gel (AcOEt/hexane 15/1) in 40% yield (mp = 110°C).
    Method B: To a cooled to −40°C solution of *t*-BuOK (0.168 g, 1.5 mmol) in THF (7 mL) a solution of **1** (1 mmol) and benzaldehyde (1.1 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred for 1.5 h at −40 to −20°C, and then quenched with water at −20°C. The product was isolated via the procedure given above. All new compounds were fully characterized. Satisfactory elemental analyses were obtained for all new compounds. Selected data:

cis-(5-Phenyl-2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl ester **4e**. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.06$ (t, $J = 7.15$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 3.52–3.74 (m, 2H), 3.85–4.08 (m, 2H), 4.52 (bdd, $J = 9.50$ Hz, $^2J_{HP} = 3.25$ Hz, 1H), 6.13 (bdd, $J = 9.50$ Hz, $^3J_{HP} = 25.00$ Hz, 1H), 7.37–7.46 (m, $5H_{arom.}$), 8.46 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = 15.98$ (d, $^3J_{CP} = 6.04$ Hz), 16.37 (d, $^3J_{CP} = 5.60$ Hz), 58.04 (d, $^1J_{CP} = 161.03$ Hz), 62.82 (d, $^2J_{CP} = 7.48$ Hz), 63.76 (d, $^2J_{CP} = 7.04$ Hz), 84.10 (d, $^2J_{CP} = 3.27$ Hz), 126.95 (s, $C_{arom.}$), 127.92 (s, $C_{arom.}$), 128.99 (s, $C_{arom.}$), 132.88 (d, $^3J_{CP} = 5.03$ Hz, $C_{arom.}$); 189.52 (d, $^3J_{CP} = 4.40$ Hz); MS-FAB $m/z = 316$ (67.5%) MH^+.

trans-(5-Phenyl-2-thioxo-oxazolidin-4-yl)phosphonic acid diethyl ester **4e**. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.26$, 1.33 (2t, $J = 7.0$ Hz, 6H), 4.06 (d, $J = 6.5$ Hz, 1H), 4.05–4.32 (m, 4H), 5.85 (dd, $J = 6.5$ Hz, $^2J_{HP} = 17.50$ Hz, 1H), 7.27–7.39 (m, $5H_{arom.}$), 8.87 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = 16.25$ (d, $^3J_{CP} = 5.72$ Hz), 16.50 (d, $^3J_{CP} = 5.25$ Hz), 60.13 (d, $^1J_{CP} = 161.90$ Hz), 63.60 (d, $^2J_{CP} = 7.19$ Hz), 64.62 (d, $^2J_{CP} = 6.94$ Hz), 83.94 (d, $^2J_{CP} = 1.64$ Hz), 125.50 (s, $C_{arom.}$), 128.92 (s, $C_{arom.}$), 129.30 (s, $C_{arom.}$), 137.32 (d, $^3J_{CP} = 9.51$ Hz, $C_{arom.}$), 188.87 (d, $^3J_{CP} = 5.3$ Hz); MS-FAB $m/z = 316$ (52.5%) MH^+.

anti-(1-*tert*-Butoxycarbonylamino-2-hydroxy-2-phenylethyl)phosphonic acid diethyl ester **7e**. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.10$, 1.31 (2bt, $J = 7.00$ Hz, 6H), 1.36 (s, 9H), 3.74–4.00 (m, 2H), 4.02–4.24 (m, 2H), 4.38 (ddd, $J = 6$ Hz, $J = 10.25$ Hz, $^2J_{HP} = 16$ Hz, 1H), 4.95 (bdd, $J = 6.0$ Hz, $^3J_{HP} = 20.25$ Hz, 1H), 5.11 (bd, $J = 10.25$ Hz, 1H), 7.27–7.44 (m, $5H_{arom.}$); ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = 15.95$ (d, $^3J_{CP} = 6.16$ Hz), 16.36 (d, $^3J_{CP} = 5.66$ Hz), 28.15 (s), 52.65 (d, $^1J_{CP} = 150.97$ Hz), 62.54 (d, $^2J_{CP} = 6.67$ Hz), 63.07 (d, $^2J_{CP} = 7.17$ Hz), 80.22 (s), 126.59 (s, $C_{arom.}$), 127.78 (s, $C_{arom.}$), 128.06 (s, $C_{arom.}$), 139.51 (d, $^3J_{CP} = 6.29$ Hz, $C_{arom.}$), 154.92 (d, $^3J_{CP} = 5.66$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$) $\delta = 23.68$; MS-FAB $m/z = 374$ (34.5%) MH^+.

syn-(1-*tert*-Butoxycarbonylamino-2-hydroxy-2-phenylethyl)phosphonic acid diethyl ester **7e**. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.27$ (bs, 9H), 1.31, 1.37 (2bt, $J = 7.00$ Hz, 6H), 4.10–4.30 (m, 4H), 4.31 (bdd, $J = 10$ Hz, $^2J_{HP} = 17.75$ Hz, 1H), 5.27 (bd, $^3J_{PNH} = 3.25$ Hz, 1H), 5.45 (bd, $J = 10.00$ Hz, 1H), 7.24–7.40 (m, $5H_{arom.}$); ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = 16.29$ (d, $^3J_{CP} = 5.72$ Hz), 28.01 (s), 52.90 (d, $^1J_{CP} = 156.30$ Hz), 62.58 (d, $^2J_{CP} = 7.04$ Hz), 63.44 (d, $^2J_{CP} = 6.86$ Hz), 71.19 (bs), 79.68 (s), 125.85 (s, $C_{arom.}$), 128.01 (s, $C_{arom.}$), 128.83 (s, $C_{arom.}$), 139.96 (d, $^3J_{CP} = 13.84$ Hz, $C_{arom.}$), 155.10 (d, $^3J_{CP} = 6.92$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$) δ 24.09, 23.41(18%, rotamer); MS-FAB $m/z = 374$ (26.4%) MH^+.

15. Similarly, for major diastereomer **4a** irradiation of H-5 produced 1.4% enhancement of H-4, indicating *trans* stereochemistry.
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