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Direct synthesis of protected diethyl 1,2-diaminoalkylphosphonates

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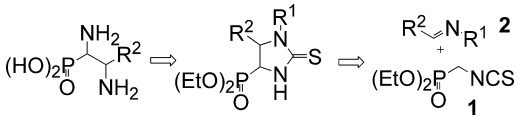
Abstract—An efficient, diastereoselective synthesis of 5-substituted (2-thioxo-imidazolidin-4-yl)phosphonic acid diethyl esters from metallated diethyl isothiocyanatomethylphosphonate and activated imines has been developed. The three-step transformation of imidazolidine-2-thione derivatives into 1,2-diaminoalkylphosphonic acids is also described.

Aminophosphonates[1,2] (phosphonate analogues of α-amino acids) have received considerable attention in bioorganic chemistry due to their unique activities as peptide mimetics, such as transition state-analogue inhibitors of human rennin,[3] HIV protease and polymerase,[4] leucine aminopeptidase[5] and serine proteases.[6] They have also been exploited as neuromodulators[1a,b] and haptens of catalytic antibodies.[1a,7] Several 1,2-diaminoalkylphosphonic acids, which can be regarded as the isosteres of α,β-diamino acids,[8] act as leucine aminopeptidase inhibitors.[9] Although a variety of strategies leading to aminophosphonates have been developed,[1a,c,2] the number of known 1,2-diaminoalkylphosphonates is limited,[1d] and only a few routes to both racemic or enantioenriched compounds have been reported. So far these aminophosphonates are available by ring-opening of aziridine phosphonic acid derivatives[10–12] with nitrogen or sulfur nucleophiles and by nucleophilic substitution of dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-mesyloxy-2-phenylethylphosphonate[13] or optically pure diethyl (3-benzyl-1,2,3-oxathiazolidine-2,2-dioxide)-4-phosphonate[14] with amines. 1,2-Diaminophosphonic acid derivatives have also been prepared by diastereoselective addition of diethyl phosphonate to chiral *O*-silylated *N*-benzylnitrones, followed by catalytic hydrogenation of the hydroxyamino phosphonates thus formed.[15] Both enantiomers of 1-substituted 1-amino-2-methylaminoethylphosphonic acids can be prepared by stereoselective alkylation of (2-*tert*-butyl-1-methyl-5-oxo-imidazolidin-4-yl)phosphonic or imidazolidinephosphonic acid dimethyl esters with organic halides, followed by reduction and acid hydrolysis.[16] In turn, enantiopure (2*R*,3*R*)-2,3-diamino-3-phosphonopropanoic acid has been obtained from the corresponding dimethyl (2*R*,3*R*)-4-oxo-3-phthalimidoazetidin-2-ylphosphonate[17] by acid hydrolysis.

Recently, we described the efficient and diastereoselective transformations of diethyl isothiocyanatomethylphosphonate[18] (**1**) into diethyl *N*-Boc 1-amino-2-hydroxyalkylphosphonates[19] and diethyl *N*-Boc 1-amino-1-alkenylphosphonates[20] via intermediate oxazolidine-2-thiones.

Herein we report further investigations in this area, utilizing diethyl isothiocyanatomethylphosphonate (**1**) and imines **2** for the synthesis of 4-phosphorylated imidazolidine-2-thiones, which can be regarded as masked diethyl 1,2-diaminoalkylphosphonates. It seems reasonable that imidazolidine-2-thiones can be useful intermediates for the synthesis of 1,2-diaminoalkylphosphonic acids (Scheme 1).

To the best of our knowledge, 1,2-diaminoalkylphosphonic acids[21] have not been obtained using this methodology[22] and the synthesis of cyclic thioureas via



Scheme 1. Retrosynthesis of 1,2-diaminoalkylphosphonic acids from isothiocyanate **1** and imines **2**.

Keywords: Nucleophilic addition; Imines; Imidazolidine-2-thiones; 1,2-diaminoalkylphosphonic acids; Diethyl isothiocyanatomethylphosphonate; Isothiocyanates.
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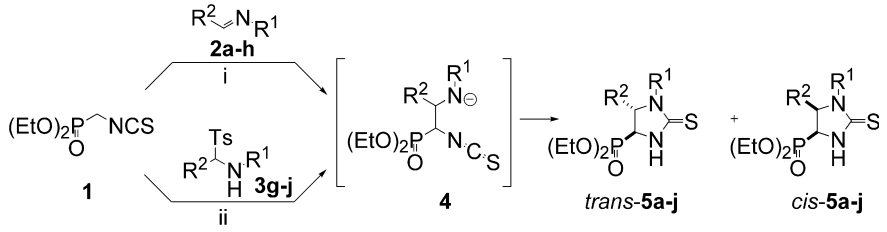


Scheme 2. Reagents and conditions: (i) method A: NaH (1.2 equiv), THF, −5–0 °C, 0.5 h, followed by aq NH_4Cl; method B: *t*-BuOK (1.2 equiv), THF, 0–5 °C, 0.5 h, followed by brine; method C: *t*-BuOK (1.2 equiv), THF, −75 °C, 2 h, followed by brine; method D: NaHMDS (1.2 equiv), THF, −75 °C, 2 h, followed by brine at −75 °C; (ii) method E: NaH (2.2 equiv), THF, 25–30 °C, 2.5 h, followed by aq NH_4Cl at 5 °C.

Table 1. Substituted imidazolidine-2-thiones **5a**–**j** prepared

Entry	Compd. **5**	R^1	R^2	Method	Yield[a] (%)	*trans*:*cis*[b]	^{31}P NMR δ (ppm) *trans*/*cis*
1	**a**	$(EtO)_2P(O)$	Ph	A	92	39:61	−3.72, 18.16/−3.82, 15.28
2	**b**	$(EtO)_2P(O)$	*p*-MeC_6H_4	A	87	38:62	−3.73, 18.21/−3.84, 15.16
3				B	64	92:8	
4	**c**	$(EtO)_2P(O)$	*p*-$MeOC_6H_4$	A	76	36:64	−3.78, 18.21/−4.21, 15.49
5				B	48	96:4	
6	**d**	Ts	Ph	A	37	50:50	16.80/14.60
7	**e**	H[c]	Ph	C	70	90:10	18.46/16.42
8	**f**	H[c]	Et	C	55	87:13	19.24/18.21
9	**g**	Boc	Ph	B	51	91:9	18.06/15.39
10				D	67	46:54	
11				E[d]	67	52:48	
12	**h**	Boc	*o*-MeC_6H_4	D	49	44:56	17.95/15.56
13				E[d]	35	39:61	
14	**i**	Boc	*p*-MeC_6H_4	E[d]	64	56:44	17.88/15.24
15	**j**	Boc	2-Furyl	E[d]	28	50:50	18.43/14.91

[a] Yields of pure, isolated products.
[b] Diastereomer ratios measured by ^{31}P NMR (101 MHz, $CDCl_3$) of the crude products.
[c] *N*-(*p*-Toluenelsulfinyl) imines **2e** and **2f** were used as substrates (entries 7 and 8, respectively). Deprotection of the sulfinyl moiety occurred under the standard work-up procedure.
[d] Sulfones **3g**–**j** were applied as synthetic equivalents of *N*-Boc imines (entries 11, 13–15).

intramolecular cyclization of isothiocyanate derivatives is rarely reported.[8,23]

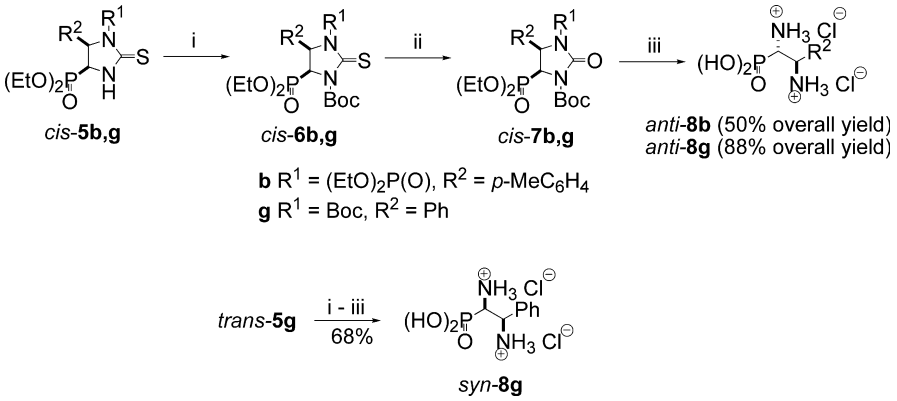
Several *N*-(diethoxyphosphoryl) imines[24] **2a**–**c**, *N*-(*p*-toluenesulfonyl) imine[25] **2d**, *N*-(*p*-toluenesulfinyl) imines[26] **2e**–**f**, *N*-Boc imines[27] **2g**–**h** as well as *N*-Boc-α-amidoalkyl-*p*-tolylsulfones[28] **3g**–**j**, which can be considered as a stable equivalents of *N*-Boc imines, were utilized as model electrophiles. The metallated diethyl isothiocyanatomethylphosphonate, prepared by deprotonation of **1** with the appropriate base (NaH, *t*-BuOK, NaHMDS), was allowed to react with imines **2a**–**h** or their precursors **3g**–**j** under conditions depending on the method used. In each case, the intermediate anion **4** formed by the initial addition participated in an intramolecular addition with the isothiocyanate function to give a mixture of racemic *trans*- and *cis*-imidazolidine-2-thiones[29] **5** (Scheme 2). The results are summarized in Table 1.

The results given in Table 1 indicate that adducts **5** are formed in moderate to excellent yields (28–92%). Diastereomeric mixtures of **5** could be easily separated into *trans*-**5** and *cis*-**5** isomers by flash chromatography on silica gel. The presented methodology is limited to aromatic aldehyde derived imines, except for *N*-sulfinyl imines, for which aliphatic analogue **2f** is also applicable. Additionally, in the case of imines **2e** and **2f**, deprotection of the sulfinyl group on nitrogen took place[30] under the standard work-up procedure, and the final products were isolated as free thioureas **5e** and **5f**.[†]

The diastereoselectivity of the reactions was base-dependent and, in principle, independent of the imines used. Thus, when NaH and NaHMDS were used as bases, thioureas **5** were formed with low diastereoselectivity (Table 1, methods A, D or E, entries 1, 2, 4 and 10–14) or formed in a non stereoselective manner (Table 1, methods A or E, entries 6 and 15). When potassium *tert*-butoxide was employed for metallation, high *trans*-diastereoselectivity (up to 92:8) was observed (Table 1, methods B and C, entries 3, 5 and 7–9). At this point, however, it is difficult to rationalize these differences.

The stereochemistry of the imidazolidine-2-thiones **5** was determined by NOE difference experiments as well

[†] When anhydrous AcOH or aq $NaHSO_4$ was used for quenching the reaction mixture, partial cleavage of the sulfinyl group occurred and a mixture of *N*-sulfinyl and free thioureas **5e** and **5f** was formed.



Scheme 3. Reagents and conditions: (i) Boc_2O (1.15 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt, 3 h; (ii) $Hg(OAc)_2$ (1.26 equiv), CH_2Cl_2, rt, 24 h; (iii) concd HCl/MeOH (8:1 v/v), reflux, 11 h.

as by examination of the vicinal coupling constants (J_{4-5}) of the ring protons H-4 and H-5. For compound *cis*-**5i**, irradiation of H-5 produced a 15.7% enhancement of the signal of H-4, indicating a *cis* relationship between those protons on the imidazolidine-2-thione ring. For compound *trans*-**5i**, irradiation of H-5 showed a 5.9% enhancement of the signal of H-4.

In addition, the estimated values of the vicinal coupling constants, 3.84 Hz for *trans*-**5i** and 9.02 Hz for *cis*-**5i**, are consistent with the observation that *trans*-imidazolidine-2-thiones[31] as well as *trans*-imidazolidine-2-ones[32] have smaller coupling constants than the corresponding *cis*-diastereomers. The same correlation has also been established for oxazolidine-2-one and oxazolidine-2-thione ring systems.[19,33] The stereochemistry of the remaining thioureas **5** was determined by comparison of the vicinal coupling constants of the major and minor isomers.

Additionally, the phosphorus chemical shifts of **5** were consistent with the appropriate given diastereomer. In the ^{31}P NMR spectra of all imidazolidine-2-thiones **5** the signals of the trans isomers appeared 2.2–3.5 ppm downfield relative to those of the cis isomers (Table 1).

Having established the synthesis of 4-phosphorylated imidazolidine-2-thiones **5**, we focused our attention on their conversion into 1,2-diaminoalkylphosphonic acids **8** (Scheme 3). A three-step transformation of **5** into acids **8** was investigated, as direct hydrolysis of the imidazolidine-2-thione ring failed.

Thus, a mixture of *trans*- and *cis*-adducts **5g**, selected as model compounds, was separated chromatographically on silica gel to give pure *trans*- and *cis*-**5g** in 30% and 32% yields, respectively. Using the standard procedure,[34] N-protection of *cis*-4-(diethoxyphosphoryl)-5-phenyl-2-thioxo-imidazolidine-1-carboxylic acid *tert*-butyl ester **5g** was achieved with di-*tert*-butyldicarbonate in the presence of DMAP to give fully protected *cis*-**6g** in 97% yield. Oxidative desulfuration of *cis*-**6g** using mercury(II) acetate[35] in dichloromethane solution provided *cis*-4-(diethoxyphosphoryl)-2-oxo-5-phenyl-imidazolidine-1,3-dicarboxylic acid di-*tert*-butyl ester **7g** in 95% yield. Finally, acid-catalyzed ring-opening of *cis*-**7g** was accomplished using concentrated hydrochloric acid in methanol (8:1 v/v).[32g,36] The desired *anti*-1,2-diamino-2-phenyl-ethylphosphonic acid **8g** was isolated in 96% yield as the dihydrochloride. The *anti*-**8b** diastereomer was obtained from *cis*-**5b** in 50% overall yield in the same way. The same sequence of reactions as above afforded *syn*-**8g** from *trans*-**5g** in 68% overall yield.

In summary, we have demonstrated that diastereoselective addition of diethyl isothiocyanatomethylphosphonate (**1**) to activated imines **2** affords 1,2-diaminoalkylphosphonates **5**, masked as cyclic thioureas. An efficient, three-step transformation of the adducts **5** into 1,2-diaminoalkylphosphonic acid dihydrochlorides **8** was also developed.

Studies to adapt this methodology for the synthesis of optically active 1,2-diaminoalkylphosphonic acids, using optically pure *N*-sulfinyl imines as chiral auxiliaries, are underway and will be reported in due course.

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29. *General procedures for the preparation of imidazolidine-2-thiones* **5**

Method A: A solution of **1** (0.209 g, 1.0 mmol) and imine **2** (1.0 mmol) in dry THF (2 mL) was added dropwise at −5 °C to a suspension of NaH (0.029 g, 1.2 mmol) in THF (6 mL). The mixture was stirred for 30 min at −5 to 0 °C and the reaction was quenched with a saturated aq solution of NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed successively with saturated aq NH_4Cl (2×2 mL), water (2 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to give crude imidazolidine-2-thiones **5**. Analytically pure trans and cis isomers of **5** were isolated after flash chromatography on silica gel.

Method B: A solution of **1** (0.209 g, 1.0 mmol) and imine **2** (1.0 mmol) in THF (2 mL) was added dropwise at 0 °C to a solution of *t*-BuOK (0.135 g, 1.2 mmol) in THF (6 mL). The mixture was stirred for 0.5 h at 0 °C and then quenched with brine (2 mL). The product was isolated via the procedure given above.

Method C: To a cooled −75 °C solution of *t*-BuOK (0.135 g, 1.2 mmol) in THF (6 mL) a solution of **1** (0.209 g, 1.0 mmol) and imine **2** (1.0 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 2 h at −75 °C and then quenched with brine (2 mL). The product was isolated via the procedure given above.

Method D: To a cooled −75 °C solution of NaHMDS (0.220 g, 1.2 mmol) in THF (6 mL) a solution of **1** (0.209 g, 1.0 mmol) and imine **2** (1.0 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 2 h at −75 °C and then quenched with brine (2 mL). The product was isolated via the procedure given above.

Method E: Powdered sulfone **3** (1 mmol) was added in one portion at rt to a suspension of NaH (0.058 g, 2.2 mmol) in dry THF (8 mL). A solution of **1** (0.209 g, 1 mmol) in THF (2 mL) was then added dropwise. The resulting mixture was stirred at 25–30 °C for 2.5 h, cooled to 5 °C and quenched with satd aq NH_4Cl (1 mL). The product was isolated via the procedure given above.

The results are summarized in Table 1. All new compounds were fully characterized. Satisfactory elemental analyses were obtained for all new compounds.

Selected data: *trans*/*cis*-**5g**: Yield: 67% (method D, *trans*/*cis* = 46/54). The mixture was separated by flash chromatography on silica gel (AcOEt/hexane, 8:1) to give *cis*-**5g** (mp = 155–157 °C) in 30% yield and *trans*-**5g** (viscous oil) in 32% yield, respectively.

cis-**5g**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.03 (t, $^3J_{HH} = 7.00$ Hz, 3H, CH_3), 1.16–1.25 (m, 12H, $CH_3 + (CH_3)_3C$), 3.19–3.32 (m, 1H, CH_2O), 3.54–3.67 (m, 1H, CH_2O), 3.90–4.02 (m, 2H, CH_2O), 4.49 (dd, $^3J_{HH} = 9.25$ Hz, $^2J_{HP} = 7.71$ Hz, 1H, CHP), 5.66 (dd, $^3J_{HH} = 9.25$ Hz, $^3J_{HP} = 5.51$ Hz, 1H, $CHCHP$), 6.96 (bs, 1H), 7.30–7.37 (m, 5H, H_{ar}); ^{13}C NMR (63 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{CP} = 3.66$ Hz), 16.3 (d, $^3J_{CP} = 6.09$ Hz,), 27.6, 55.4 (d, $^1J_{CP} = 170.56$ Hz), 62.8 (d, $^2J_{CP} = 6.09$ Hz), 62.9 (d, $^2J_{CP} = 7.31$ Hz), 64.3, 83.5, 127.6, 128.7, 129.1, 136.5 (d, $^3J_{CP} = 6.09$ Hz), 149.1, 181.6 (d, $^3J_{CP} = 12.18$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$): δ 15.39; MS-FAB *m*/*z* (%): 413.4 (100%), $M-H^+$; Anal. Calcd for $C_{18}H_{27}N_2O_5PS$ (414.46): C, 52.16; H, 6.57; N, 6.76. Found: C, 51.91; H, 6.64; N, 6.42.

trans-**5g**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (s, 9H, $(CH_3)_3C$), 1.36 (t, $^3J_{HH} = 7.25$ Hz, 3H, CH_3), 1.37 (t, $^3J_{HH} = 7.25$ Hz, 3H, CH_3), 3.79 (d, $^3J_{HH} = 3.75$ Hz, 1H, CHP), 4.25 (quin, $^3J_{HH} = {}^3J_{HP} = 6.75$ Hz, 4H, CH_2O),

5.55 (dd, $^3J_{HH} = 3.75$ Hz, $^3J_{HP} = 19.65$ Hz, 1H, C*H*CHP), 7.24–7.29 (m, 2H, H_{ar}), 7.31–7.40 (m, 3H, H_{ar}), 7.53 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 16.5 (d, $^3J_{CP} = 6.09$ Hz), 16.6 (d, $^3J_{CP} = 6.09$ Hz), 27.7, 57.9 (d, $^1J_{CP} = 158.4$ Hz), 63.6 (d, $^2J_{CP} = 7.31$ Hz), 64.0, 64.2 (d, $^2J_{CP} = 7.31$ Hz), 83.5, 125.6, 128.2, 128.6, 140.6 (d, $^3J_{CP} = 12.18$ Hz), 149.4, 178.4 (d, $^3J_{CP} = 10.96$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$): δ 18.06; MS-FAB *m*/*z* (%): 413.4 (100%), $M-H^+$; Anal. Calcd for $C_{18}H_{27}N_2O_5PS$ (414.46): C, 52.16; H, 6.57; N, 6.76. Found: C, 51.87; H, 6.81; N, 6.51.

anti-**8g**: Overall yield: 88%; yellow solid (mp = 230–236 °C); ^{1}H NMR (250 MHz, D_2O): δ 3.79 (bt, $^3J_{HH} \approx {}^2J_{HP} \approx 11.65$ Hz, 1H, C*H*P), 4.48–4.59 (m, 1H, C*H*C_{arom}), 7.45 (s, 5H_{arom}); ^{13}C NMR (63 MHz, D_2O): δ 47.5 (d, $^1J_{CP} = 131.57$ Hz), 51.9, 126.3, 128.4, 129.0 (d, $^3J_{CP} = 12.18$ Hz), 129.3; ^{31}P NMR (101 MHz, D_2O): δ 9.59; MS-FAB *m*/*z* (%): 217.1 (70%), M^+-2HCl; Anal. Calcd for $C_8H_{15}Cl_2N_2O_3P$ (289.10): C, 33.24; H, 5.23; N, 9.69. Found: C, 33.62; H, 5.51; N, 9.91.

syn-**8g**: Overall yield: 68%; white solid (mp = 248–253 °C); ^{1}H NMR (250 MHz, D_2O): δ 3.91 (dd, $^3J_{HH} = 5.71$ Hz, $^2J_{HP} = 14.73$ Hz, 1H, C*H*P), 4.90 (dd, $^3J_{HH} = 5.71$ Hz, $^3J_{HP} = 16.68$ Hz, 1H, C*H*C_{arom}), 7.48 (s, 5H_{arom}); ^{13}C NMR (63 MHz, D_2O): δ 48.0 (d, $^1J_{CP} = 134.01$ Hz), 51.7, 125.8, 127.7, 128.5, 128.7 (d, $^3J_{CP} = 4.87$ Hz); ^{31}P NMR (101 MHz, D_2O): δ 8.57; MS-FAB *m*/*z* (%): 217.1 (74%), M^+-2HCl; Anal. Calcd for $C_8H_{15}Cl_2N_2O_3P$ (289.10): C, 33.24; H, 5.23; N, 9.69. Found: C, 33.59; H, 5.62; N, 10.00.

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