COMMUNICATION

Novel approach to the synthesis of α-alkoxycarbonyl α-aminophosphonic esters based on a facile transformation of phosphoranes to phosphonic esters

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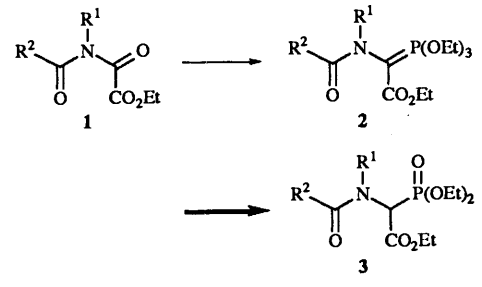
Triethoxyphosphoranes 2, generated *in situ* from oxamates 1, reacted with bromotrimethylsilane to give α-aminophosphonic esters 3 which, in the case of example 13, have been used in a new synthesis of 1-β-methylcarbapenem 14.

α-Aminophosphonic esters have attracted considerable attention as enzyme inhibitors[1] and haptens for catalytic antibodies.[2] Their utility as the substrates for the Horner–Wadsworth–Emmons reaction (HWE reaction) has also been well documented in the synthesis of dehydroamino acids,[3] peptides,[4] β-lactams[5] and other heterocycles[6] of pharmaceutical interest.

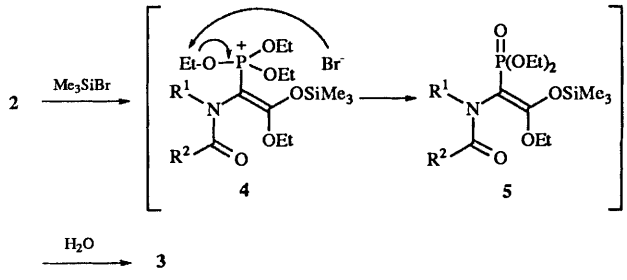
A variety of the α-aminophosphonic esters has been prepared, using the Arbusov[7] or Michaelis–Becker[8] reactions or related processes.[5a,9] There are, however, some difficulties in the preparation of the starting materials, concerning yield and procedure. Even recent approaches require multiple step syntheses[7c] and/or the handling of hazardous chemicals.[9b] Therefore, more convenient and versatile synthetic methods are still in demand.

In cases where the appropriate carbonyl compounds have electron-withdrawing groups at the α-position, such as in oxamates **1**, treatment of the ketones with triethyl phosphite give the triethoxyphosphoranes **2** directly *via* reactive carbene intermediates (Scheme 1).[10] We report herein a novel and efficient method for transforming these triethoxyphosphoranes **2** to α-aminophosphonic esters **3** with bromotrimethylsilane and its application to the synthesis of a 1-β-methylcarbapenem **14**.



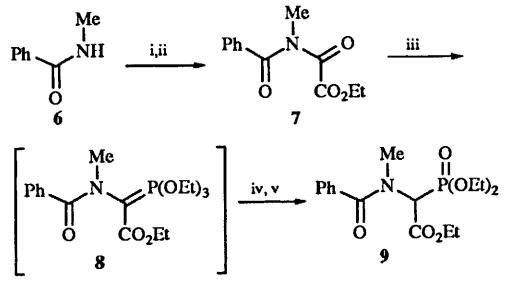
Scheme 1

Thermolytic[10a,e] and hydrolytic[10b,e] pathways have been shown to convert the triethoxyphosphoranes **2** into the α-aminophosphonic esters **3**, though the processes so far have not been synthetically satisfactory because of poor yields and the limited substrates obtainable. As an alternative route to the α-aminophosphonic esters **3**, we suggested converting **2** into **3** as depicted in Scheme 2. If bromotrimethylsilane were to effect *O*-silylation of the ester carbonyl group of **2**, the liberated bromide anion could then counter-attack[11] one of the ethoxy groups on phosphorus in **4** to afford the ketene silylacetal **5**. After hydrolysis of **5**, the desired α-aminophosphonic esters **3** might be obtained.



Scheme 2

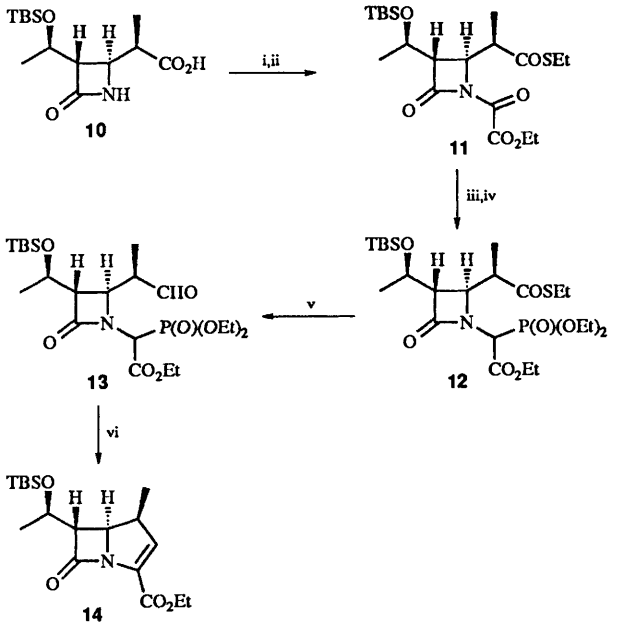
This proposal was tested with the triethoxyphosphorane **8** selected as a typical example, as shown in Scheme 3. Treatment



Scheme 3 *Reagents and conditions:* i, $NaN(SiMe_3)_2$, THF, −78 °C, 1 h; ii, $ClCOCO_2Et$, −78 °C, 1 h, 54%; iii, $P(OEt)_3$, toluene, reflux 7 h; iv, Me_3SiBr, 10 °C, 5 min; v, H_2O, quant.

of *N*-methylbenzamide **6** with sodium bis(trimethylsilylamide) followed by acylation with ethyl oxalyl chloride gave the oxamate **7**. Conversion of **7** into the triethoxyphosphorane **8** was accomplished using a modified Schering's protocol[10c] by heating **7** under reflux with triethyl phosphite (3 equiv.) in toluene. Since the triethoxyphosphorane **8** was too unstable to be isolated by silica gel column chromatography, the crude product, which was characterized by SIMS spectroscopy, was used directly for the next reaction. Addition of bromotrimethylsilane (1.3 equiv.) to **8** in toluene at 10 °C and subsequent aqueous work-up yielded the desired diethyl phosphonate **9** in essentially quantitative yield (based on **7**) after purification by silica gel column chromatography. The ^1H NMR spectrum of **9** at 25 °C showed minor signals (*ca.* 24%) at δ_H 4.9 (d, *J* 26 Hz, methine) and 3.23 (s, methyl). They are assigned to an amide rotamer, since the signals completely disappeared in the ^1H NMR spectrum at 45 °C.[12]

To demonstrate the utility of the present methodology, the synthesis of the 1-β-methylcarbapenem **14** was undertaken as shown in Scheme 4. The commercially available propionylazetidinone **10** was used to form a thioester which was then acylated with ethyl oxalyl chloride, to give the oxamate **11** (95%). Application of the present methodology to the substrate



Scheme 4 *Reagents and conditions:* i, EtSH, CDI, CH_3CN, 25 °C, 17 h, quant.; ii, $ClCOCO_2Et$, Et_3N, THF, 10 °C, 1 h, 95%; iii, $P(OEt)_3$, toluene, reflux, 7 h; iv, Me_3SiBr, toluene, 10 °C, 2 h, 87%; v, Et_3SiH, Pd–C, CH_2Cl_2, 10 °C, 1 h, 57%; vi, Pr^i_2EtN, LiCl, CH_3CN, 25 °C, 17 h, 88%

11 afforded the diethyl phosphonate **12** in 87% yield.† The thioester of **12** was then converted into the aldehyde **13** without accompanying epimerization using Fukuyama's procedure.[13] Aldehyde **13** gave 1-β-methylcarbapenem **14** smoothly in 88% yield, using the HWE reaction and applying Masamune's conditions.‡[14] To the best of our knowledge, this is the first example where the carbapenem skeleton has been constructed using the HWE reaction.§ The utility of **14** as a versatile intermediate for the synthesis of the 1-β-methylcarbapenems has been shown in the literature.[17]

In conclusion, we have found a novel and efficient method for synthesizing the biologically interesting diethyl α-aminophosphonates based on the bromotrimethylsilane mediated counter-attack reaction with triethoxyphosphoranes. The synthesis of the 1-β-methylcarbapenem **14** exemplifies the usefulness of the present methodology in providing HWE reagents for the synthesis of various heterocycles including carbon analogues of natural β-lactams with intriguing biological activities.¶

† **12**: colourless syrupy oil; ν_{max}(Nujol)/cm^{-1} 1767 and 1681; δ_H($CDCl_3$) 4.80 (d, *J* 23 Hz) and 4.79 (d, *J* 25 Hz) (1 H), 3.79–3.82 and 3.94–4.25 (m, 8 H), 2.84–3.19 (m, 2 H), 2.78 (q, *J* 7.4 Hz, 2 H), 1.11–1.31 (m, 18 H), 0.78–0.80 (m, 9 H) and −0.14–0.00 (m, 6 H); SIMS *m*/*z* 358 (M^+ + 1).

‡ **14**: colourless syrupy oil; ν_{max}(KBr)/cm^{-1} 1783 and 1727; δ_H($CDCl_3$) 6.25 (d, *J* 2.6 Hz, 1 H), 4.07–4.24 (m, 4 H), 3.16–3.21 (m, 1 H), 3.14 (ddq, *J* 2.8, 10.2 and 7.4 Hz, 1 H), 1.24 (t, *J* 7.1 Hz, 3 H), 1.17 (d, *J* 6.2 Hz, 3 H), 1.04 (d, *J* 7.4 Hz, 3 H), 0.80 (s, 9 H) and 0.001 (s, 6 H); δ_C($CDCl_3$) 175.08, 160.85 (2s), 134.82 (d), 134.60 (s), 86.43 (d), 61.31 (t), 60.31, 57.67, 38.50 (3d), 23.75, 22.41 (2q), 18.01 (s), 18.50, 14.14, −4.18 and −4.90 (4q); SIMS *m*/*z* 354 (M^+ + 1). The stereochemical assignment of the C-1-β-methyl group of **14** was confirmed by the NOESY spectroscopy; sharp cross peaks were observed between 1-H and 5-H, the C-1-methyl group and 6-H, respectively. In addition, the coupling constant between 1-H and 5-H (10.2 Hz) of **14** was in good agreement with the reported value (10.1 Hz).[15]

§ For other methodologies to construct the 1-β-methylcarbapenem skeleton, see ref. 16 and references cited therein.

¶ Recently, C-2 unsubstituted penems have been reported to be promising candidates for a new class of chemotherapeutic agents which exhibit potential inhibitory activities to a leader peptidase in *Escherichia coli*.[18] The compound **14** can be regarded as a carbon analogue of these inhibitors.

Experimental

Typical reaction procedure for ethyl *N*-benzoyl-*N*-methylamino-(diethoxyphosphoryl)acetate 9

A mixture of oxamate **7** (1.0 g, 4.3 mmol) and triethyl phosphite (2.2 cm^3, 13 mmol) in toluene (10 cm^3) was heated under reflux for 7 h under a nitrogen atmosphere. The mixture was then evaporated under reduced pressure and co-evaporated twice with toluene (30 cm^3 × 2) to afford 1.97 g of crude **8** as a colourless oil [characterized by SIMS: *m*/*z* 386 (M^+ + 1)]. The residue was dissolved in toluene (10 cm^3) and treated with bromotrimethylsilane (0.85 cm^3, 6.5 mmol) at 10 °C. The mixture was stirred for 5 min, after which it was poured into water (30 cm^3) and extracted twice with EtOAc (30 cm^3 × 2). The combined extracts were washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1 to 1:1) to afford **9** (1.57 g, quant.) as a colourless oil ν_{max}(Nujol)/cm^{-1} 1746 and 1648; δ_H($CDCl_3$) 7.32–7.50 (m, 5 H), 6.08 and 4.90 (d, *J* 26 Hz, 1 H), 4.04–4.37 (m, 6 H), 3.17 and 3.23 (s, 3 H) and 1.30–1.42 (m, 9 H); δ_C($CDCl_3$) 172.18 (s), 166.16 (ds, J_{PC} 6 Hz), 135.27 (s), 130.03, 128.52, 127.1 (3d), 63.61 (dt, J_{PC} 5.7 Hz), 63.10 (dt, J_{PC} 6.9 Hz), 62.18 (t), 55.45 (dd, J_{PC} 152 Hz), 36.43 (q), 16.44 (dq, J_{PC} 5.9 Hz) and 16.15 (dq, J_{PC} 6.6 Hz); SIMS *m*/*z* 358 (M^+ + 1).

Acknowledgements

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