Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 4432

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COMMUNICATION

Alkenylphosphonates: unexpected products from reactions of methyl 2-[(diethoxyphosphoryl)methyl]benzoate under Horner–Wadsworth–Emmons conditions†

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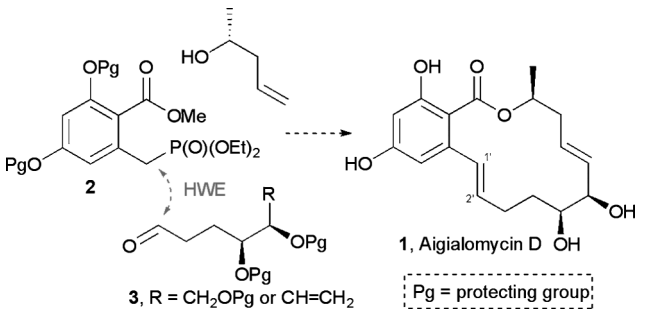
Received 31st March 2011, Accepted 27th April 2011
DOI: 10.1039/c1ob05506b

Methyl 2-[(diethoxyphosphoryl)methyl]benzoate reacts with several aldehydes to produce an alkenylphosphonate as the major product, together with varying amounts of the expected Horner–Wadsworth–Emmons product, a 1,2-disubstituted *E*-alkene. Use of a bulky aldehyde or the *tert*-butyl ester favours the normal HWE product.

The Horner–Wadsworth–Emmons (HWE) variation of the Wittig reaction is one of the most utilised transformations in organic chemistry; it involves the coupling of a β-stabilised phosphonate anion with an aldehyde to form an *E*-alkene.[1] The mechanism is well understood[2] and modifications that select for the kinetic product, the *Z*-alkene, have been developed.[3] The precise ratio of *E*- to *Z*-isomers depends on the identity of the base, the structures of aldehyde and phosphonate, the reaction temperature and the solvent.[4] Asymmetric versions that operate by kinetic resolution processes, and HWE reactions in sequence with other reactions, are also known.[5] If there is no carbanion-stabilising group (usually a carbonyl) at the β-position of the phosphonate partner, the HWE reaction often does not proceed to completion, giving stable β-hydroxyphosphonates instead. However, a method to eliminate β-hydroxyphosphonates provides a reliable multi-step variant of the HWE.[6] 2-(Methoxycarbonyl)benzylphosphonates represent a form of vinylogous β-carboxyphosphonates and might be expected to behave in a similar manner to the normal HWE substrates. Indeed, a number of examples demonstrating the HWE reaction of benzylic phosphonates exist in the literature.[7,8,9,10] During an early stage of our research on the total synthesis of aigialomycin D (**1**),[11] HWE reaction between a 2-(methoxycarbonyl)benzylphosphonate **2** and a sugar-derived aldehyde **3** appeared to be a viable method for formation of the C1′–C2′ *E*-olefin (Scheme 1).

Our initial appraisal of the HWE reaction in the synthesis of aigialomycin D focussed around model studies using a simple 2-(methoxycarbonyl)benzylphosphonate lacking aromatic oxygen substituents. Thus, methyl 2-[(diethoxyphosphoryl)methyl]benzoate (**4**)[7,8,12] was prepared by bromination[13] of commercially available methyl 2-methylbenzoate (**5**) followed by an Arbuzov reaction of benzylic bromide **6** with triethylphosphite (Scheme 2). It was found that purification of the bromide intermediate **6** was unnecessary, due to the lack of reactivity of the by-products (mostly the benzylic dibromide) with triethylphosphite. Treatment of **4** with various bases and sugar-derived aldehydes **3** led to decomposition of the aldehydes and some recovery of starting material **4**. To deconvolute the impact of the carbohydrate functional groups, we investigated the reaction of **4** with simple model aldehydes. Thus, treatment of a cold (–78 °C) ethereal solution of benzylphosphonate **4** with lithium bis(trimethylsilylamide) (LiHMDS) and subsequent addition of octanal (**7a**) provided the expected HWE product, *E*-alkene **8a** (Scheme 2). The spectroscopic data from this material were consistent with its structure, namely the presence of mutually coupled (J = 15.7 Hz) olefinic peaks at 7.12 and 6.14 ppm indicative of a *E*-disubstituted alkene, together with the expected aromatic, aliphatic and methyl ester signals. However, the yield was low (7%) and the ^{1}H NMR spectrum of the crude reaction mixture had indicated the presence (and dominance) of another olefinic species. Further acidification and extraction of the aqueous washings generated during work up of the reaction led to the isolation of a highly polar material, assigned the structure *E*-**9a** (Scheme 2). The ^{1}H NMR spectrum of this compound displayed a one-proton signal at 6.72 ppm (dt, J = 23.1, 7.3 Hz) that exhibited COSY correlations only with signals in the aliphatic region. The 23 Hz coupling constant is consistent with three-bond ^{1}H–^{31}P



Scheme 1 Proposed HWE route to aigialomycin D (**1**).

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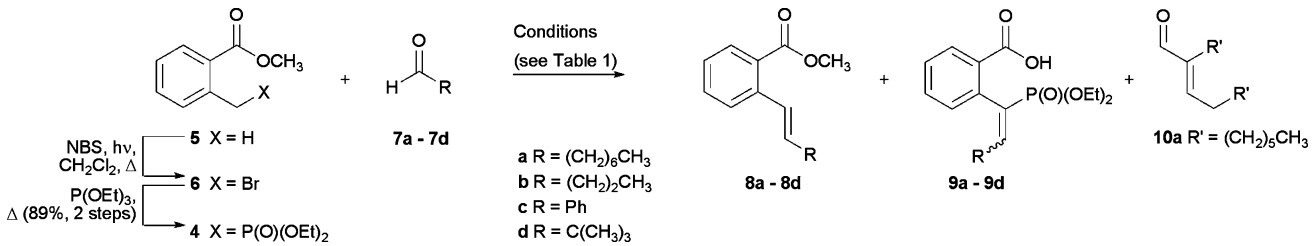
† Electronic supplementary information (ESI) available: Procedures for all reactions and spectroscopic data for all new compounds, ^{1}H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/c1ob05506b

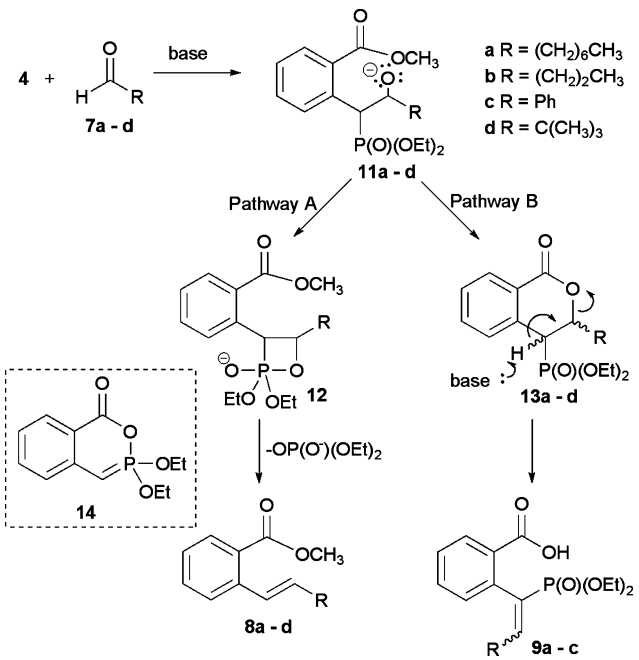


Scheme 2 Synthesis of methyl 2-[(diethoxyphosphoryl)methyl]benzoate (**4**) and its reactions with aldehydes **7a–7d**.

interactions in a *cis*-relationship within an alkenylphosphonate.[14] In addition, appropriate aliphatic and aromatic peaks accounting for the remainder of the structure were observed in the spectrum. Notably, the methyl ester singlet was absent from the spectrum and a broad hump was observed in the low-field region, indicating the presence of a carboxylic acid instead. HRMS analysis confirmed the molecular formula of the assigned structure **9a**.

The reaction was then repeated with a range of conditions and several different aldehydes, as described in Table 1. In all cases except that involving pivaldehyde (entry 12), the major product was the alkenylphosphonate *E*-**9** (entries 1–11). The corresponding *Z*-isomer was also present in minor amounts in some of the crude reaction mixtures but it has not yet been isolated; its main distinguishing feature by NMR was the much larger $^{3}J_{H,P}$ of 48 Hz.[14] In the octanal reactions (entries 1–6), an additional by-product was noted in variable amounts whose spectral data match those of α,β-enal **10a**, the self-condensation product of octanal.[15] There was a trend in the effect of the solvent on the outcome, such that increasing the polarity generally increased the preference for formation of the alkenylphosphonate (entries 1–3 and 7–8). Performing the reaction at a higher temperature seemed to decrease slightly the preference for the alkenylphosphonate product (entries 3 *vs.* 5). The ratio of alkene to alkenylphosphonate was also dependent on the counterion to the base (entries 3 *vs.* 4). Use of methoxide as the base also favoured the alkenylphosphonate (entries 6 and 11). The reactions with benzaldehyde produced significant quantities of the alkenylphosphonate *E*-**9c** (entries 9–11), but not its *Z*-isomer. It is noteworthy that the sterically bulky pivaldehyde gave exclusively the disubstituted alkene product **8d** in excellent yield (entry 12).

Mechanistically, formation of the alkenylphosphonates **9** may arise from the normal HWE intermediate **11** (Scheme 3). Pathway A gives the expected HWE product, alkene **8**, by elimination of oxaphosphetane **12**. The alternative mechanism, pathway B, in which the oxyanion of **11** attacks the ester, is available for this vinylogous ester but not for β-carboxyphosphonates (the normal



Scheme 3 Proposed mechanisms of product formation.

Table 1 Reactions of methyl 2-[(diethoxyphosphoryl)methyl]benzoate (**4**) with aldehydes

Entry	Aldehyde	Conditions	Ratio of **8** : *E*-**9** : *Z*-**9**[a]	Yield of **8**[b]	Yield of *E*-**9**[b]
1	**7a**	LiHMDS, Et_2O, –78 °C	13 : 81 : 6	7%	57%
2	**7a**	LiHMDS, toluene, –78 °C	22 : 78 : 0	12%	49%
3	**7a**	LiHMDS, THF, –78 °C	0 : 79 : 21	0%	71%
4	**7a**	KHMDS, THF, –78 °C	45 : 55 : 0	(33%)[c]	(41%)[c]
5	**7a**	LiHMDS, THF, 0 °C	13 : 66 : 21	(8%)[c]	28% (34%)[c]
6	**7a**	NaOMe, THF, 0 – 67 °C	0 : 100 : 0	(0%)[c]	(42%)[c]
7	**7b**	LiHMDS, Et_2O, –78 °C	*ca.* 30 : 70 : 0	21%	31%
8	**7b**	LiHMDS, toluene, –78 °C	*ca.* 35 : 65 : 0	24%	21%
9	**7c**	LiHMDS, THF, –78 °C	15 : 85 : 0	11%	37%
10	**7c**	LiHMDS, toluene, –78 °C	7 : 93 : 0	(5%)[c]	(64%)[c]
11	**7c**	NaOMe, THF, 0 – 67 °C	29 : 71 : 0	(8%)[c]	(21%)[c,d]
12	**7d**	LiHMDS, THF, –78 °C	100 : 0 : 0	88%	0%

[a] Ratios were calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yields except where otherwise stated. [c] Numbers in brackets are NMR yields, calculated from ^{1}H NMR spectra of the crude reaction mixtures and included for cases where the isolated yields were not obtained. [d] Poor conversion was noted in this reaction, possibly due to the quality of NaOMe used.

Table 2 Reactions of *tert*-butyl ester **15** with octanal (**7a**)

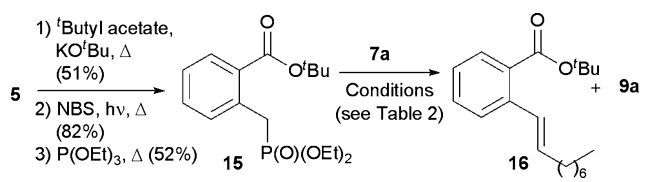
Entry	Conditions	Ratio **16** : **9a**[a]	Yield **16**[b]	Yield *E*-**9a**
1	LiHMDS, THF, –78 °C	67 : 33	41% (45%)[c]	(23%)[c]
2	KHMDS, THF, –78 °C	80 : 20	(55%)[c]	(14%)[c]
3	NaO^{t}Bu, THF, 0 – 67 °C	100 : 0	31%	0%

[a] Ratios were calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yields except where otherwise stated. [c] Numbers in brackets are NMR yields, calculated from ^{1}H NMR spectra of the crude reaction mixtures and included for cases where the isolated yields were not obtained.

HWE substrates). Pathway B produces the lactone **13** and leads, upon eliminative opening of the lactone ring, to the observed alkenylphosphonates **9**. Steric minimisation during this process would favour the *E*-alkenylphosphonates over the *Z*-isomers. The precise roles of solvent and temperature in controlling the product distribution are presently unclear. An alternative mechanism involving the cyclic phosphonate **14**[16] was ruled out by performing a control reaction in which the phosphonate **4** was treated with LiHMDS in THF at –78 C in the absence of an aldehyde; after quenching with aqueous hydrochloric acid and extracting, only unmodified starting material was obtained.

The result obtained with pivaldehyde (R = *tert*-butyl) indicates that a bulky R group inhibits formation of the lactone **13d**, instead leading exclusively to the expected disubstituted alkene **8d**, in good yield (88%), *via* the normal HWE mechanism. This implies that the transition state leading to **13** is more crowded than for the oxaphosphetane **12**, as borne out by a simple visual inspection of the structures.

Based on the mechanism outlined above, it seems reasonable to propose that the lactonisation step of pathway B (*viz.* **11** to **13**) would be disfavoured in systems with higher electron density in the aromatic ring (and correspondingly at the carbonyl centre) and, therefore, that the HWE pathway would dominate. This correlates well with literature precedent, in which more electron-rich, phenolic benzylphosphonates are reported to produce HWE products reliably and in good yields.[9] Use of a bulky ester might also be expected to disfavour pathway B. This hypothesis was probed by treating the *tert*-butyl ester equivalent of **4**, *viz.* compound **15**‡ (Scheme 4), with LiHMDS and octanal under the same conditions as entry 3, Table 1. A mixture of alkene **16** and alkenylphosphonate *E*-**9a**, was obtained in a 2 : 1 ratio (Table 2, entry 1). This proportion of alkene to alkenylphosphonate contrasts markedly with the exclusive formation of the latter (**9a**) by reaction of the methyl ester **4** under the same reaction conditions. As with the methyl ester, use of KHMDS increased the preference for the alkene (entry 2). Furthermore, treatment of **15** with sodium *tert*-butoxide and octanal produced only the normal HWE product, alkene **16** (entry 3). None of the *Z*-alkenylphosphonate *Z*-**9a** was observed in the reactions of **15**. These results indicate that the bulky ester group prevents lactone formation (*viz.* **13a**, Scheme 3) and directs the mechanism through the HWE pathway.



Scheme 4 Synthesis of *tert*-butyl ester **15**[17] and its reactions with octanal.

Optimisation of the conditions that select for the alkenylphosphonates would allow efficient preparation of these interesting products that have potential utility as synthetic intermediates[18] and biologically active compounds.[19]

Conclusions

Observation of alkenylphosphonates **9** as dominant products in the reactions of phosphonate **4** with several aldehydes has led to a proposed mechanism that involves intermediacy of the phosphonolactone **13**. This process competes with the normal HWE mechanism in reactions of 2-(methoxycarbonyl)benzylphosphonates with straight-chain and aromatic aldehydes, which explains the variability of yields in their reported HWE reactions.[7,8,9] Addition of steric bulk to the aldehyde or ester shuts down this competing pathway and allows efficient preparation of the normal HWE products.

Acknowledgements

Funding was gratefully received from the Foundation for Research, Science and Technology (NZ) for a Bright Futures PhD Scholarship (LJB). The Faculty of Science at Victoria University is thanked for financial support.

Notes and references

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