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An improved synthesis of α-phosphonoenamines based on a modified Peterson olefination

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Abstract—An efficient, stereoselective method for the synthesis of α-phosphonoenamines based on a modified Peterson olefination is described. The carbanion derived from isolatable intermediate **2** reacts with aromatic or aliphatic aldehydes selectively eliminating in Peterson fashion to deliver functionally rich α-phosphonoenamines **3**. The synthetic utility of these enamines is demonstrated by their hydrolysis yielding the homologous carboxylic acids in good yield.
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1. Introduction

Approaches towards the synthesis of α-amino phosphonates **1** (Fig. 1) and derivatives[1,2] have been intensely investigated over the last few decades with applications as peptide-mimics due to their homology with the corresponding α-amino acids. Not surprisingly, these compounds are inhibitors of a range of proteolytic enzymes and derivatives have now been shown to exhibit a wide range of biological properties,[1] including antibacterial activity.[3] On the other hand, the related α,β-unsaturated-α-phosphonoenamines such as **3** (Fig. 1) have received considerably less synthetic attention,[4,5] although some have also been shown to possess biological activity.[6] The syntheses of these latter compounds have been achieved mainly from α-aminodiphosphonates[4] using carbanion chemistry, however these procedures provide low (29–47%) to moderate (average 55%) yield of the desired α-phosphonoenamine intermediate as (*E*)/(*Z*) mixtures, in part due to the sensitivity of the enamine functionality.

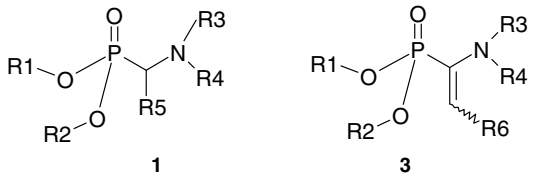

Figure 1. General α-aminophosphonate **1** and α-phosphonoenamine **3** structures.

A reliable, high yielding synthesis of α-phosphonoenamines **3** has hindered application-development of these derivatives. Gross and Costisella reported the hydrolysis of these intermediates to give homologated carboxylic acids,[4d] work later extended by Degenhardt[4e] employing the diphosphonate route. This appears to be a potentially valuable synthetic interconversion (aldehyde to homologated acid) although it has been rarely applied due to the difficulty in accessing the necessary phosphonoenamine intermediate. Finally, a significant advance was reported by Dufrechou and co-workers wherein excess base and trimethylsilyl chloride were employed to trap α-aminophosphonate/aldehyde adducts undergoing in situ Peterson-type elimination.[7] The dense functionality found in α-phosphonoenamines **3** in conjunction with the commercially available α-*N*,*N*-dimethylaminophosphonate **1** stimulated our interest in developing the aldol-type reaction shown (Scheme 1) as a route to phosphonoenamines. In this Letter, we report that while the direct reaction of enolate derivatives of **1** with aldehydes is problematic, the trimethylsilyl derivative of this compound **2** can be prepared and isolated and that it readily enters into the reactions with both aromatic and aliphatic aldehydes in Peterson fashion to yield α-phosphonoenamines in high yield. These intermediates undergo ready hydrolysis in aqueous HBr extending the carbonyl-homologation strategy

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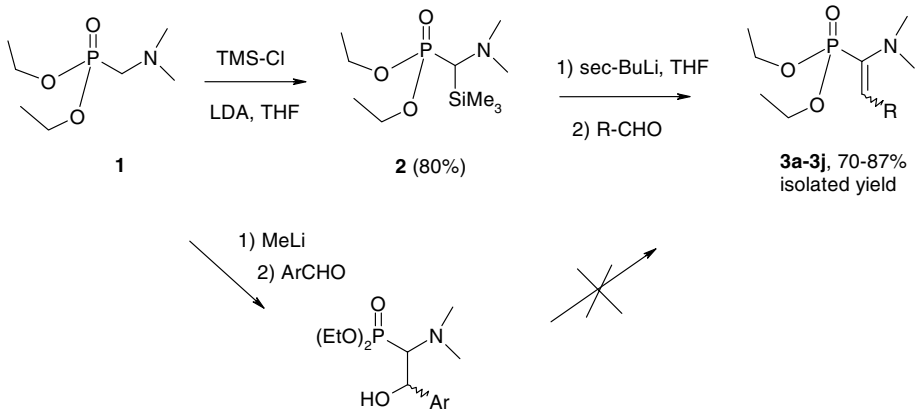


Scheme 1.

(aldehyde to homologated carboxylic acid) to a range of aromatic and aliphatic carboxylic acids.[4d]

2. Results and discussion

On the one hand, the direct aldolization of various enolate derivatives of **1** with aromatic aldehydes or ketones provided α-phosphonoenamines **3** only in low yield. For example, reaction of the anion of **1** (formed with MeLi, THF, −78 °C) with 4-chlorobenzaldehyde or acetone gave the corresponding β-hydroxyl-α-aminophosphonate adducts in moderate yields of 67% (two diastereomers) and 60%, respectively. Attempts to dehydrate these intermediates to the α-phosphonoenamines gave complex mixtures resulting in poor yields of **3**. The failure to selectively dehydrate these intermediates prompted us to attempt a Peterson variant of the reaction using a functionalized α-silyl carbanion.[8] To this end, we prepared the α-trimethylsilyl derivative **2** (Scheme 1) employing a silylation strategy first described by Padwa et al. in the silylation of cyanoamines.[9] In the present case, rapid N-silylation of **1** with trimethylsilylchloride gave the trimethylsilyl ammonium salt. Deprotonation with LDA promoted the desired N to C migration of the trimethylsilyl group most likely via a nitrogen ylide intermediate. The trimethylsilyl intermediate **2** proved to be stable to silica gel and could be stored under argon for several days without decomposition. The intermediate was however readily hydrolyzed back to the starting aminophosphonate **1** when treated with aqueous acid. Formation of the α-silyl carbanion from the above intermediate **2** using *sec*-BuLi in THF (−78 °C) and the addition of piperonal, as outlined in Scheme 1, to our delight led to the formation of the corresponding phosphonoenamine **3a** with 95% conversion and 87% isolated yield. Although the precise mechanism of the Peterson reaction is still unclear (so-called betaine versus oxasiletanide intermediates)[8] the present intermediate, shown as the betaine (Fig. 2), selected the Peterson elimination pathway over the Horner–Emmons route. Vinylsilanes are also possible products from this reaction and this 'challenge' unambiguously demonstrates the prominence of the Peterson pathway,[7] reactivity also observed with simple α-silylphosphonates.[8]

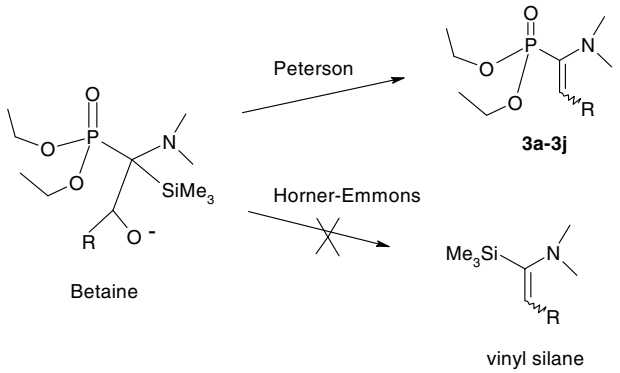


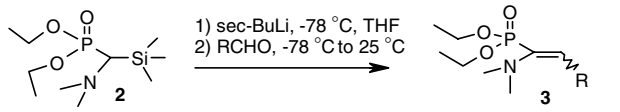
Figure 2. Possible pathways for elimination from the α-silylated 'betaine-type' intermediate.

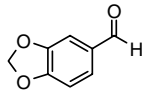
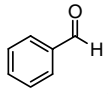
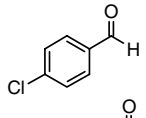
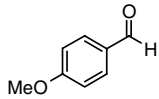
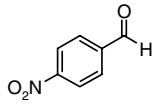
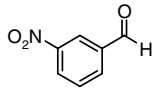
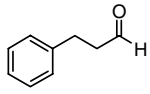
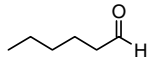
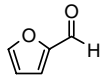
The scope of the reaction was investigated with a range of aromatic and aliphatic aldehydes the results of which are summarized in Table 1.

Conversions are high in all cases with isolated yields being only slightly lower. Under these conditions of kinetic control, aromatic aldehydes provided a mixture of (*E*)/(*Z*) olefins that rapidly isomerize to give exclusively the thermodynamically more stable (*E*)-isomers. No significant electronic effect was observed with both electron rich and electron poor derivatives reacting equally well (entries 1–6). In the case of aliphatic aldehydes, dihydro-cinnamaldehyde (entry 7) provided a single (*E*)-adduct, most likely as the kinetic product, while other aliphatic aldehydes gave (*E*)/(*Z*) mixtures (entries 8 and 9). These isomers could be separated and proved to be configurationally stable. The heteroaryl aldehyde 2-furfural also yielded its corresponding adduct efficiently (entry 10).

Although the reactivity of α-phosphonoenamines remains largely been unexplored (vide supra) the obvious synthetic potential of the homologation strategy prompted our further interest. The use of boiling hydrochloric acid was reported to give carboxylic acids through initial enamine hydrolysis and cleavage of the derived α-ketophosphonate intermediate.[4d] Three examples of this homologation were reported by Gross and

Table 1. Peterson reaction of α-trimethylsilyl-α-dimethylamino-phosphonate with aldehydes



Entry	RCHO		Conversion (%)[a] **3**	Isolated yield of **3**[b] (%)	*E*:*Z*[c]
1		(**2a**)	>95 **3a**	87	100:0
2		(**2b**)	>90 **3b**	67	100:0
3		(**2c**)	>94 **3c**	80	100:0
4		(**2d**)	>95 **3d**	85	100:0
5		(**2e**)	>95 **3e**	82	100:0
6		(**2f**)	>95 **3f**	80	100:0
7		(**2g**)	>90 **3g**	75	100:0
8		(**2h**)	>90 **3h**	70	60:40
9		(**2i**)	>90 **3i**	70	65:35
10		(**2j**)	>95 **3j**	75	100:0

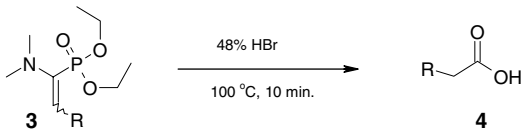
[a] Conversion is based on the recovered aldehyde partner.

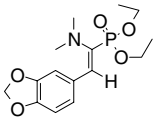
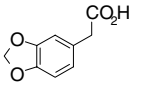
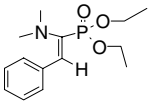
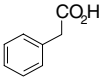
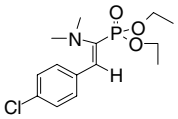
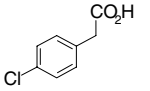
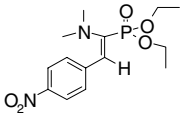
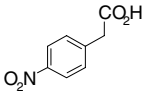
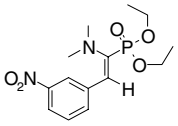
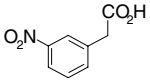
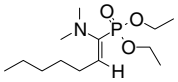
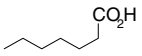
[b] Isolated yield of the phosphonoenamine **3** after chromatographic purification.

[c] The (*Z*)-isomer derived of aromatic aldehydes fully converts to the (*E*)-isomer, see text. In the case of aliphatic aldehydes, both configurational isomers were separated.

Costisella[4d] and the route appears to have been applied only once.[4e] The protocol is perhaps underutilized due to the difficulties in accessing intermediates **3** and the need for optimization of the conditions for enamine hydrolysis, which produces ketophosphonate intermediates and also results in decarboxylation with β-aryl acids.[4e] Investigation of the hydrolysis of adduct **3a** under various conditions revealed that high yields of the hydrolysis product could be obtained under a tightly held set of conditions. Treatment of the piperonal adduct **3a** with 48% HBr and gentle warming to 100 °C with a heat-gun led to rapid hydrolysis and isolation of the homologous acid in 90% yield (Table 2, entry 1). Longer heating time gives very poor yield of the homologated acid, presumably due to rapid decarboxylation, whereas shorter heating time gives only α-ketophosphonate. The use of HBr under these reaction conditions proved to be general for both electron rich and electron deficient aryl derivatives (Table 2, entries 2–5) with high yields of carboxylic acid being obtained in all cases. Lastly, the hexanal derived α-phosphonoenamine **3f** was readily hydrolyzed to heptanoic acid (Table 2, entry 6) extending the scope to aliphatic derivatives also.

Table 2. Hydrolysis of α-phosphonoenamines to provide the corresponding homologous carboxylic acids



Entry	Phosphonoenamine		**4** Isolated yield (%)	
1		(**3a**)		(**4a**) 90
2		(**3b**)		(**4b**) 93
3		(**3c**)		(**4c**) 95
4		(**3d**)		(**4d**) 98
5		(**3e**)		(**4e**) 97
6		(**3f**)		(**4f**) 90

While several well-known carbonyl homologation strategies are employed in synthetic chemistry, most involve several steps to extend an aldehyde or ketone to the homologated aldehyde. The present two-step method appears to be potentially useful as in the overall process, an aldehyde is converted into the homologous carboxylic acid **4** via the intermediacy of **3**. Few other methods have been reported to effect this precise transformation (aldehyde to homologated acid).[10] Furthermore, the method allows efficient conversion of common aldehydes to phenylacetic acid and substituted derivatives which are valuable industrial intermediates in the production of pharmaceuticals, cosmetics and fragrances.[11]

3. Conclusion

In conclusion, we describe the synthesis and isolation of an α-silyldimethylaminophosphonate **2** and reaction of its anion with aldehydes yielding α-phosphonoenamines. The scope of the Peterson route to α-phosphonoenamines **3** described herein is wide and an expanded range of derivatives are now available using this methodology in higher yields than previous related methods and with high (*E*)-selectivity.[6,7] While certain of these derivatives have been prepared using the Horner–Emmons olefination reaction of diphosphonates,[4] the greater efficiency of the Peterson olefination likely derives from the higher oxygenophilicity of silicon versus phosphorus,[8] enabling milder reaction conditions and minimizing the decomposition of labile α-phosphonoenamines **3**. An optimized protocol is described for the hydrolysis of these intermediates in warm hydrobromic acid which appears to be a general method for the overall conversion of both aromatic and aliphatic aldehydes into the homologous carboxylic acid derivatives. Work in our laboratories continues with the exploration of the reactivity of α-phosphonoenamines with a view to expanding their chemical utility and will be reported in due course.

4. Experimental

Synthesis of **2**. Into a 20 mL flame-dried round bottom flask, containing a magnetic stirring bar, was added diethyl *N*′,*N*-dimethylaminophosphonate (500 μL, 4.128 mmol) under argon. To this was added dry THF (8.26 mL). The contents were cooled to −78 °C and stirred for 15 min. whereupon TMS–Cl (550 μL, 4.349 mmol) was added to the reaction flask over 5 min. Upon stirring for 30 min., a solution of LDA (2.5 mL, 5.0 mmol, 2 M, THF) was added slowly to the reaction flask maintained at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 6 h. The resulting mixture was concentrated to remove solvent. Water was added (10 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The product, $R_f = 0.32$ (EtOAc, pink-red to ninhydrin), was purified by silica gel column chromatography (EtOAc). The silica gel was neutralized by adding five drops of triethylamine into the initial silica gel slurry. The title compound **2**, 882.2 mg (80%) was isolated as a brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.14 (s, 9H); 1.33 (t, $J_{HH} = 6.4$ Hz, 6H); 2.38 (d, $J_{PH} = 22.2$ Hz, 1H); 2.47 (s, 6H); 4.07 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.6 (d, $J = 2.5$ Hz); 16.5 (dd, $J = 6.30$, 2.5 Hz); 45.5 (d, $J = 3.8$ Hz); 55.3 (d, $J = 112.5$ Hz); 60.7 (t, $J = 7.8$ Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 30.75; HRMS $(M)^+$ calcd. for $C_{10}H_{26}N_1O_3SiP$: 267.1421, found: 267.1420.

General procedure for Table 1: Synthesis of **3a**. Into a flame-dried flask, containing a magnetic stirring bar, was weighed compound **2** (74.0 mg, 0.278 mmol) under argon and dry THF (556 μL) added to make a 0.5 M solution. The flask was stirred for 15 min. at −78 °C whereupon *sec*-BuLi (239 μL, 0.334 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of piperonal (50 mg, 0.333 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature where it was stirred for further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification using silica gel column chromatography (EtOAc) yielded **3a**, 79.1 mg, (87%) as a yellow semisolid. R_f (EtOAc): 0.36. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, $J_{HH} = 7.0$ Hz, 6H); 2.65 (d, $J_{PH} = 2.0$ Hz, 6H); 4.13 (m, 4H); 5.94 (s, 2H); 6.67 (d, $J_{PH} = 14.86$ Hz, 1H); 6.75 (d, $J_{HH} = 7.8$ Hz, 1H); 7.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, $J = 6.8$ Hz); 43.1 (d, $J = 2.3$ Hz); 61.6 (d, $J = 5.6$ Hz); 101.1; 107.9; 109.3; 125.0; 129.4; 130.9 (d, $J = 31.8$ Hz); 137.8 (d, $J = 182.1$ Hz); 147.3; 147.5; ^{31}P NMR (80 MHz, $CDCl_3$): δ 18.0; HRMS $(M)^+$ calcd. for $C_{15}H_{22}NO_5P$: 327.1237; found: 327.1236.

General procedure for Table 2: Synthesis of **4a**. Into a flame dried flask was weighed phosphonoenamine **3a** (50 mg, 0.158 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 min. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over ($MgSO_4$), filtered and concentrated to yield **4a**, 26.8 mg, (95%); off-white solid, mp 125–127 °C; CAS registry number [2861-28-1].

Acknowledgements

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References and notes

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