Pergamon

Tetrahedron Letters 42 (2001) 125–128

TETRAHEDRON LETTERS

The solid phase synthesis of unsymmetrical phosphinic acids

Philip B. Cox,* Vincent M. Loh, Jr., Claude Monteils, Anthony D. Baxter and E. Andrew Boyd

Discovery Division, Oxford Asymmetry International plc, 111 Milton Park, Milton, Abingdon, Oxon OX14 4RX, UK

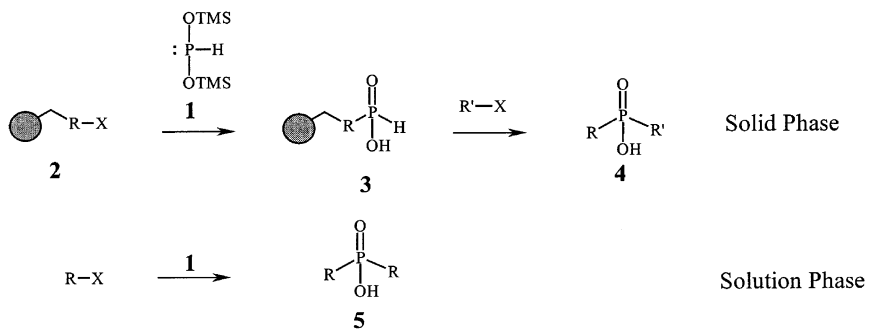
Received 29 August 2000; accepted 26 October 2000

Abstract—This letter describes a method for the synthesis of unsymmetrical phosphinic acids by the phosphinylation of a resin-bound aldehyde and subsequent 'P' alkylation. This synthetic transformation is very difficult to perform as selectively in solution and therefore further exemplifies the powerful nature of solid phase organic chemistry (SPOC). © 2000 Published by Elsevier Science Ltd.

It is now firmly recognised that solid phase organic chemistry (SPOC) is a powerful tool for the high throughput synthesis of broad structural classes of chemical libraries for use in high throughput screening programmes—generally the start of the drug discovery process. Since the pioneering work of Merrifield in the early 1960s, the use of solid phase chemistry remained largely confined to peptide synthesis until the early 1990s when the emergence of combinatorial chemistry prompted a solid phase chemistry renaissance.[1] This technology has now evolved to an extent where a plethora of chemistries can be performed on solid supports.[2]

Of the many advantages that SPOC presents, one of the most useful facets of this technology is the ability to produce unsymmetrical compounds, very selectively, from symmetrical substrates; something that is often very difficult to achieve in solution. We have recently taken advantage of this to synthesise the dihydropteridinone heterocycles[3] and, more recently, for the assembly of a range of novel unsymmetrical phosphinic acids.

The phosphinic acid motif is an important constituent of both biologically active natural products[4a] and pharmaceuticals, for example fosinopril and fosinoprilat (a phosphinate ester) are used in the clinical management of hypertension.[4b] Phosphinic acids have been the subject of a number of syntheses in the literature in recent years, both in solution[5a] and on solid phase.[5b] Our strategy for the assembly of these compounds relied on the clean addition of the symmetrical reagent BTSP **1** to the electrophilic resin **2** to produce the immobilised phosphinic acids **3** (Scheme 1). Further alkylation, this time with the electrophile in solution, and cleavage off resin, should facilitate the formation of the desired unsymmetrical phosphinic acid **4**. This strategy is often very difficult to implement in solution,[5a] as the initial phosphorylation with BTSP often leads to undesired dimerization; the formation of the symmetrical bis-substituted phosphinic acid **5**.

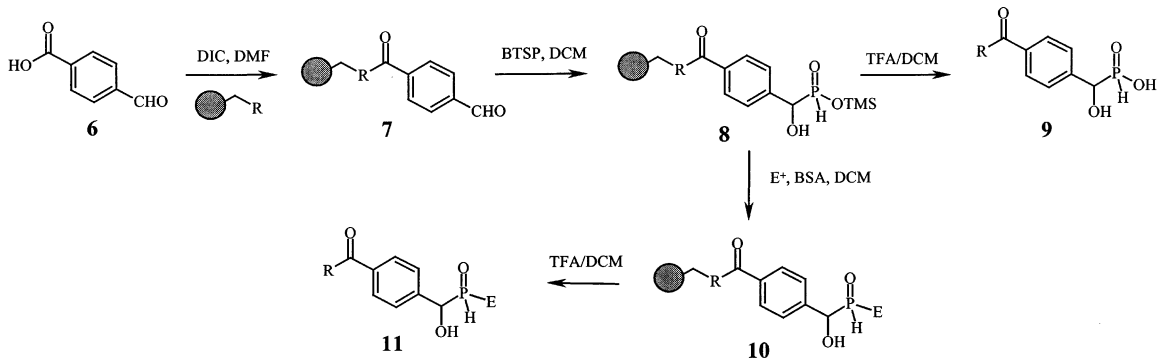


Scheme 1.

Keywords: solid phase organic chemistry (SPOC); bis-trimethylsilylphosphonite (BTSP); phosphinic acids.

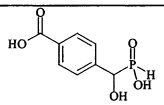
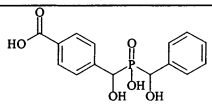
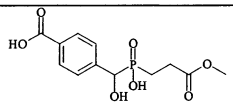
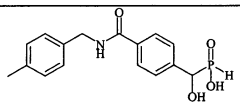
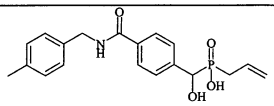
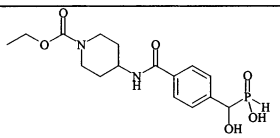
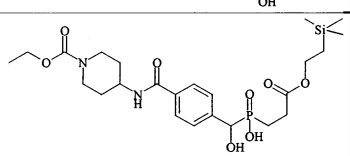
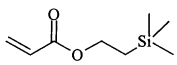
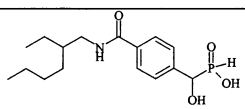
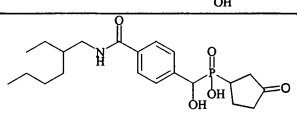
* Corresponding author. E-mail: pcox@oai.co.uk

0040-4039/01/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01897-9



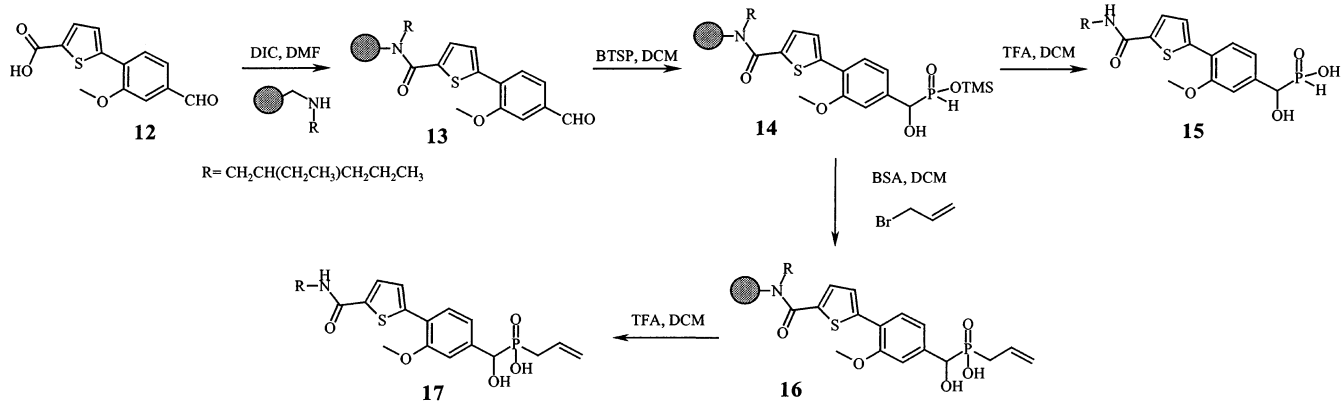
Scheme 2.

Table 1.

Entry	Phosphinic Acid Products	E^+	% Purity, Yield	$\delta^{31}P$ NMR
1		N/A	100, 70	30.8
2			61, 95	39.5, 41.3
3			63, 95	47.8
4		N/A	83, 95	31.6
5			85, 95	45.5
6		N/A	70, 45	30.6
7			100, 95	48.1
8		N/A	60, 73	33.4, 29.7
9			73, 95	48.4, 50.4

To test this hypothesis we focussed on the addition of BTSP to resin-bound aryl aldehydes. Thus as a model, 4-formyl benzoic acid **6** was coupled up to both Wang[6] resin and a functionalised Ameba[7] resin under standard conditions. The aldehyde was then treated with a solution of BTSP in DCM overnight (Scheme 2).

Cleavage of the resin bound phosphinic acid **8** at this stage with TFA revealed that clean addition to the aldehyde had occurred to give the required products **9**.[8] In order to extend the scope of this chemistry, by introducing a further point of diversity into the molecule, we focussed on performing 'P' alkylation with a variety



Scheme 3.

of electrophiles to form a new phosphorus–carbon bond; thereby producing the required bis-substituted unsymmetrical phosphinic acids **10**. Thus, nucleophilic addition to aldehydes and α,β-unsaturated ketones led to the formation of the desired alcohols **11** (entries 2 and 9, Table 1) with the products formed, in each case, as a 1:1 mixture of diastereomers. Nucleophilic addition to α,β-unsaturated esters, and allylation, worked very well to supply the desired Michael adducts (entries 3 and 7, Table 1) and allyl phosphinic acid (entry 5, Table 1), respectively.[9] The possibility of using other formyl-carboxylate containing building blocks was also explored using rather more sophisticated heterobiaryl carboxy-aldehyde building blocks (Scheme 3).

Thus the carboxy-aldehyde **12** was coupled to a functionalised Ameba resin to give the resin-bound aldehyde **13**. To this was added BTSP, as a solution in DCM, and the suspension stirred at room temperature overnight. Cleavage at this stage (80% TFA/DCM) revealed that clean addition to the aldehyde had occurred to form the phosphinic acid **15** (95% yield, 100% purity by LCMS, integration at 215 nm). Further functionalisation was then performed by treating the resin-bound phosphinic acid **14** with a solution of allyl bromide and BSA in DCM overnight to give the immobilised bis-substituted phosphinic acid **16**. Cleavage of the product off resin (80% TFA/DCM) and analysis by LCMS and NMR revealed that the desired unsymmetrical phosphinic acid **17** was produced very cleanly (95% yield, 100% purity by LC–MS, integration at 215 nm).

In conclusion, we have demonstrated that it is possible to use SPOC to synthesise novel unsymmetrical mono and bis-substituted unsymmetrical phosphinic acids very selectively, something that is generally very difficult to perform in solution.

Acknowledgements

We thank the Analytical Department at OAI for MS, LC, and LC/MS analysis. We also wish to thank Dr. C. Holyoke, Dr. S. Lee, and Dr. M. Howard of DuPont Agricultural Products for helpful discussions.

References

1. Merrifield, R. B. *Sci. Am.* **1968**, *218* (3), 56–62.
2. For examples of comprehensive reviews on combinatorial and solid supported chemistry, see: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *30*, 8135–8173. (b) Balkenhohl, F.; Bussche-Huennefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288–2337. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, 449–472. (d) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998. (e) Bunin, B. A. *The Combinatorial Index*; Academic: San Diego, 1998. (f) Obrecht, D.; Villalgordo, V. B. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Elsevier Science: Oxford, 1998.
3. Baxter, A. D.; Boyd, E. A.; Cox, P. B.; Loh, V.; Monteils, C.; Proud, A. *Tetrahedron Lett.* **2000**, *41*, 8177–8181.
4. (a) Zeiss, H.-J. *Pestic. Sci.* **1994**, *41*, 269–277. (b) Murdoch, D.; McTavish, D. *Drugs* **1992**, *43*, 123–140.
5. For some examples of phosphinic acid assembly, see: Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223–4226. Boyd, E. A.; Boyd, M. E. K.; Loh, V. M. *Tetrahedron Lett.* **1996**, *37*, 1651–1654. Boyd, E. A.; Chan, W. C.; Loh, V. M. *Tetrahedron Lett.* **1996**, *37*, 1647–1650. Dorff, P. H.; Chiu, G.; Goldstein, S. W.; Morgan, B. P. *Tetrahedron Lett.* **1998**, *37*, 3375–3378. Haaf, K.; Patek, M. *German Patent* **1999**, DE 19745628.
6. Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333.
7. Fivush, A. M.; Willson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151.
8. General experimental method for the formation of the resin-bound mono-substituted phosphinic acid: The resin-bound aldehyde was pre-swollen in a minimum volume of DCM. A solution of BTSP (1 mM, 10 equiv.) in DCM was added under Ar, and the mixture agitated for 16 h. The reaction was then filtered and washed with equal volumes of DCM, methanol, DCM, methanol, DCM and ether. The resin was then dried in a stream of air for 15 min. A sample of resin was cleaved with the 80% TFA in DCM for 0.5 h and the sample evaporated to dryness.

9. General experimental procedure for the formation of the resin-bound unsymmetrical bis-substituted phosphinic acid: The resin-bound mono-substituted phosphinic acid was pre-swollen in a minimum volume of degassed DCM. BSA (20 equiv.) was added under Ar, and the mixture agitated for 2 h. The electrophile (20 equiv.) was added to the mixture, which was then agitated for a further 16 h. The reaction was then filtered and washed with equal volumes of DCM, methanol, DCM, methanol, DCM and ether. The resin was then dried in a stream of air for 15 min. A sample of resin was cleaved with 80% TFA in DCM for 0.5 h.