

A new approach to peptide synthesis

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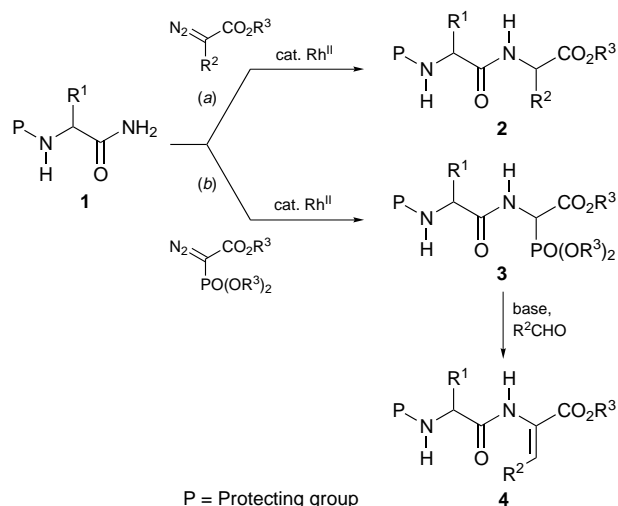
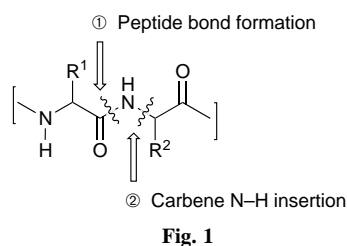
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A new approach to the synthesis of dipeptides is described based on the formation of the NHCHR¹CONH–CHR²CO bond by carbenoid N–H insertion, rather than the formation of the peptide bond itself.

Peptides and proteins play a central role in all living organisms, and hence the synthesis of such compounds has emerged as a subject in its own right.¹ In fact peptide synthesis is so highly developed that chemists rarely, if ever, consider any approach other than the formation of the amide bond (Fig. 1, disconnection 1). We now report a new approach to peptide synthesis which involves formation of the CONH–CHR²CO bond by a metal carbenoid N–H insertion reaction (Fig. 1, disconnection 2), and its application in the synthesis of dipeptides of dehydro amino acids, including the protected dehydro dipeptide component of the tunicchrome Mm-2.

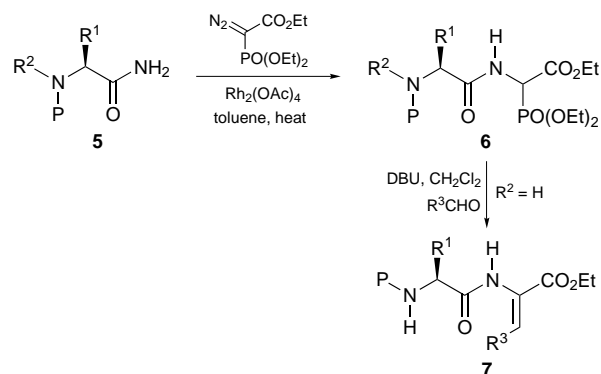
The N–H insertion reactions of metallocarbenoids, first described in 1952,² have found use in synthesis particularly in the construction of bicyclic β-lactams.³ We have recently described the application of such N–H insertion reactions in the preparation of α-amino acids, α-aminophosphonates and phosphonoglycines,^{4,5} and therefore were attracted by the possibility of using carbenoid N–H insertions in a synthesis of dipeptides which, unusually, does not rely on formation of the peptide bond itself. Two approaches starting from readily available *N*-protected amino acid amides **1** were considered (Scheme 1). Firstly, the use of diazo esters which would lead directly to dipeptides **2** [Scheme 1(a)]. There is one reported example of this approach which resulted in the synthesis of *Z*-Phe-α,α,α-trifluoroAla-OMe **2** (P = Z, R¹ = Bn, R² = CF₃, R³ = Me) from methyl 2-diazo-3,3,3-trifluoropropionate,⁶ and we have used both methyl 2-diazo-2-phenylacetate and methyl 2-diazo 3-oxobutanoate to give dipeptides **2** (R² = Ph and Ac respectively).^{7,8} In the latter case the dipeptides **2** (R² = Ac) were cyclodehydrated to give oxazoles.^{8,9} The second approach, which is reported herein, involves the rhodium(II)-catalysed reaction of diazophosphonoacetate to give phosphonates **3**, Wadsworth–Emmons reaction of which leads to the dehydro dipeptide **4** [Scheme 1(b)].

The key N–H insertion reaction was carried out by treating a mixture of the *N*-protected amino acid amide **5** and triethyl diazophosphonoacetate with a catalytic amount of rhodium(II) acetate in toluene, and resulted in the formation of the phosphonates **6** in good yield (Scheme 2, Table 1). The N–H insertion reaction was completely regioselective, in that no competing insertion into the carbamate N–H bond was



Scheme 1

observed. Although related phosphonates have been prepared previously by synthesis of the corresponding α-amino-phosphonate followed by peptide coupling,¹⁰ the simplicity of this new method gives it some advantages. Wadsworth–Emmons reaction of the phosphonates **6** with a range of aldehydes using DBU as base¹¹ gave the corresponding dehydro dipeptides **7** in good yield (Scheme 2, Table 2). In each case a



Scheme 2

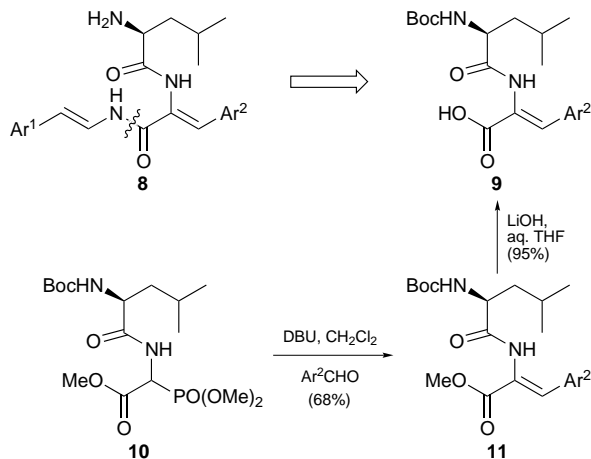
Table 1 Formation of phosphonates **6** from amides **5**

Amide	P	R ¹	R ²	Phosphonate	Yield (%)
5a	Z	H	H	6a	81
5b	Boc	Me	H	6b	88
5c	Z	Me	H	6c	80
5d	Boc	Pr ⁱ	H	6d	80
5e	Boc	Bu ⁱ	H	6e	82
5f	Z	–(CH ₂) ₃ –		6f	80

Table 2 Formation of dehydro dipeptides **7** from phosphonates **6**

Phosphonate	P	R ¹	R ³	Dehydro dipeptide	Yield (%)
6a	Z	H	Ph	Z-Gly- Δ Phe-OEt	7a 82
6b	Boc	Me	Ph	Boc-Ala- Δ Phe-OEt	7b 88
6c	Boc	Bu ⁱ	Ph	Boc-Leu- Δ Phe-OEt	7c 88
6e	Boc	Bu ⁱ	Pr ⁱ	Boc-Leu- Δ Leu-OEt	7d 82
6e	Boc	Bu ⁱ	Ar ^a	Boc-Leu- Δ Trp-OEt	7e 80

^a Ar = *N*-Boc-indol-3-yl.

**Scheme 3**

single diastereoisomer was formed which on the basis of literature precedent was assigned the *Z*-configuration.

Finally, the new approach to dipeptides was applied to the synthesis of the dehydro dipeptide fragment of Mm-2 **8** (Ar¹ = Ar² = 3,4-dihydroxyphenyl), a blood pigment of the tunicate *Molgula manhattensis*.¹² Although this compound has been synthesised previously,¹² the projected disconnection

(Scheme 3) to the protected dehydro dipeptide **9** (Ar² = 3,4-dibenzyloxyphenyl) differs from the published strategy. The phosphonate **10**, prepared from *N*-Boc-leucinamide and trimethyl phosphonoacetate in exactly the same way as its triethyl analogue **6e**, reacted readily with 3,4-dibenzyloxybenzaldehyde to give the required dipeptide **11** (Ar² = 3,4-dibenzyloxyphenyl) as a single *Z*-diastereomer. Hydrolysis of ester **11** gave the required acid **9** in 95% yield (Scheme 3).

In summary, we have shown that carbenoid N–H insertion reactions can be applied in a new approach to peptides which does not involve the formation of the peptide bond itself; such an approach may offer advantages in some cases.

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Footnote and References

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- For example, J. Jones, *The Chemical Synthesis of Peptides*, Clarendon, Oxford, 1991.
- P. Yates, *J. Am. Chem. Soc.*, 1952, **74**, 5376.
- For a compilation of references, see ref. 4.
- E. Aller, R. T. Buck, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson and J. B. Sanghera, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2879.
- L. Ferris, D. Haigh and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2885.
- S. N. Osipov, N. Sewald, A. F. Kolomiets, A. V. Fokin and K. Burger, *Tetrahedron Lett.*, 1996, **37**, 615.
- C. J. Moody and R. T. Buck, unpublished results.
- M. C. Bagley, R. T. Buck, S. L. Hind, C. J. Moody and A. M. Z. Slawin, *Synlett*, 1996, 825.
- C. J. Moody and M. C. Bagley, *Synlett*, 1996, 1171.
- U. Schmidt and B. Riedl, *Synthesis*, 1993, 815.
- U. Schmidt, H. Griesser, V. Leitenberger, A. Lieberknecht, R. Mangold, R. Meyer and B. Riedl, *Synthesis*, 1992, 487.
- D. Kim, Y. Li, B. A. Horenstein and K. Nakanishi, *Tetrahedron Lett.*, 1990, **31**, 7119.

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