A new approach to peptide synthesis

Christopher J. Moody,[a,b] Leigh Ferris,[b] David Haigh[c] and Elizabeth Swann[a]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, Devon, UK EX4 4QD*
[b] *Department of Chemistry, Loughborough University, Loughborough, Leicestershire, UK LE11 3TU*
[c] *Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park (North), Coldharbour Road, The Pinnacles, Harlow, Essex, UK CM19 5AD*

A new approach to the synthesis of dipeptides is described based on the formation of the NHCHR[1]CONH–CHR[2]CO 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 for formation of the CONH–CHRCO bond by a metal carbene 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 tunichrome 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, R^1 = Bn, R^2 = CF_3, R^3 = 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** (R^2 = Ph and Ac respectively).[7,8] In the latter case the dipeptides **2** (R^2 = 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

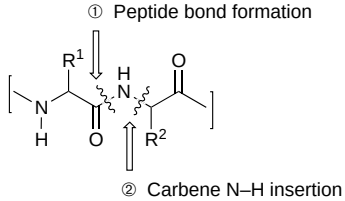
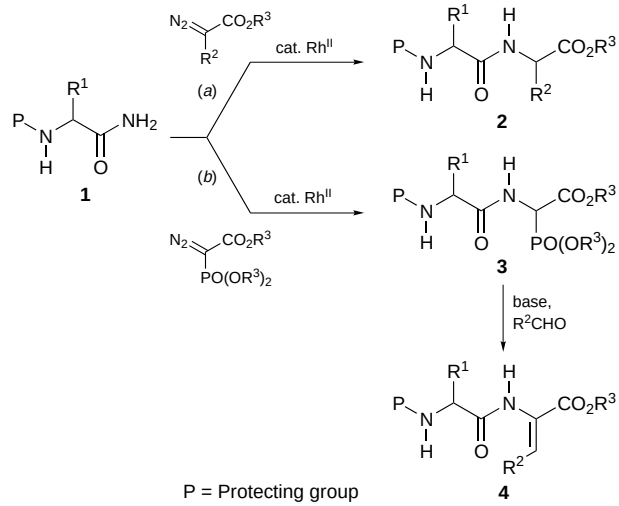
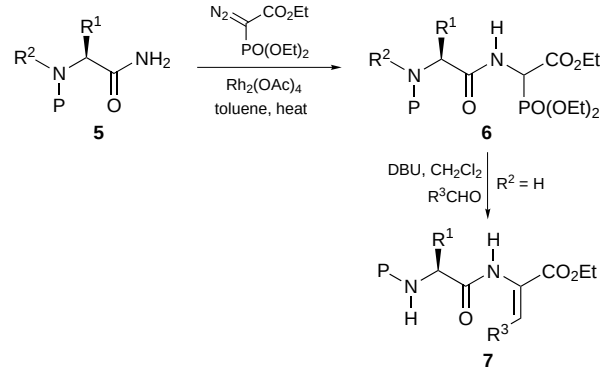


Fig. 1



Scheme 1

observed. Although related phosphonates have been prepared previously by synthesis of the corresponding α-aminophosphonate 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 base[11] gave the corresponding dehydro dipeptides **7** in good yield (Scheme 2, Table 2). In each case a



Scheme 2

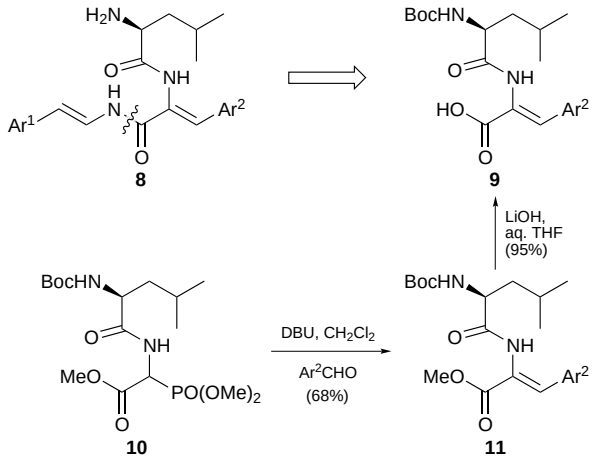
Table 1 Formation of phosphonates **6** from amides **5**

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-ΔPhe-OEt	**7a**	82
6b	Boc	Me	Ph	Boc-Ala-ΔPhe-OEt	**7b**	88
6e	Boc	Bu^i	Ph	Boc-Leu-ΔPhe-OEt	**7c**	88
6e	Boc	Bu^i	Pr^i	Boc-Leu-ΔLeu-OEt	**7d**	82
6e	Boc	Bu^i	Ar[a]	Boc-Leu-ΔTrp-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** (Ar^1 = Ar^2 = 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** (Ar^2 = 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** (Ar^2 = 3,4-dibenzyloxyphenyl) as a single *Z*-diasteromer. 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.

We thank Loughborough University and SmithKline Beecham Pharmaceuticals for their support.

Footnote and References

* E-mail: c.j.moody@exeter.ac.uk

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

Received in Cambridge, UK, 15th September 1997; 7/06658I