Organophosphorus Esters of 1-Hydroxy-2-phenylbenzimidazole: Synthesis and Utilization as Novel Peptide Coupling Reagents

Nagnnath D. Kokare,[a,b] Rahul R. Nagawade,[a,b] Vipul P. Rane,[a,b] Devanand B. Shinde*[a]

[a] Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004 (MS), India

[b] Wockhardt Research Centre, New Drug Discovery, Aurangabad 431210 (MS), India
E-mail: dbschemtech@hotmail.com

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Abstract: Highly efficient coupling reagents – phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester, diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester and phosphoric acid diphenyl ester 2-phenylbenzimidazol-1-yl ester – were designed, synthesized and successfully applied in peptide coupling reactions. Their efficiency was evaluated through the synthesis of a range of amides and peptides, and the extent of racemization was studied by HPLC and found to be negligible. The mechanism of action is probably similar to those found for organophoshorus esters of hydroxybenzotriazole: a presumption supported by the isolation and characterization by mass spectrometry and ^{1}H NMR of some of the proposed intermediates.

Key words: *N*-hydroxy-2-phenylbenzimidazole, peptide coupling reagents, HOBt, amide synthesis, minimal racemization

A commonly encountered problem in peptide synthesis involves an extensive racemization of the amino acid component, usually through oxazolone formation, undesired side reactions and low coupling rates.[1–3] Thus a combination of high efficiency during the formation of the amide bond, together with a low level of racemization of the coupled components, represent the main objectives in the development of new coupling reagents. Over the last few years, a number of new coupling reagents have been reported in the literature that have shown considerably improved coupling ability over more traditional methods involving carbodiimide. Generally, in order to prevent the loss of configuration, additives such as 1-hydroxybenzotriazole (**1a**; HOBt)[4] or 7-aza-1-hydroxybenzotriazole (**1b**; HOAt)[5] have been used. Such reagents have also been used in many protocols for stepwise peptide assembly, either in conjunction with carbodiimide[6] or active esters,[7] or through incorporation into stand-alone reagents such as phosphonium[8] or uronium/guanidinium salts.[9] Currently preferred coupling reagents include organophosphorus derivatives of HOBt and 3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODht), which includes diethoxyphosphinyloxybenzotriazole (**2**; DepOBt),[10] 3-(diethoxyphosphinyloxy)-3,4-dihydro-4-oxo-1,2,3-benzotriazine (**3**; DepODht),[11] 3-*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-3,4-dihydro-4-oxo-1,2,3-benzotriazine (**4**; DopODht),[12] 1,2-benzisoxazolyl diphenyl phosphate,[13] 3-phenoxyphosphinyloxy-3,4-dihydro-4-oxo-1,3-quinazoline (**5**),[13] 1-diphenoxyphosphinyloxy-2-oxopyridine (**6**),[14] BOP **7a**[15] and AOP **7b**[16] (Figure 1). During peptide coupling via uronium and phosphonium salts, the N-protected amino carboxylic acid first reacts with the coupling reagent to give an active ester, which then reacts with an amino component to give the corresponding amide. The latter step is rate-limiting and responsible for loss of configuration. The inherent reactivity of the active ester intermediate is therefore a critical aspect of particular uronium or phosphonium salts. In connection with our ongoing research, we have designed and synthesized the organophosphorus esters of substituted benzimidazoles and demonstrated their ability to act as amide and peptide coupling reagents with minimal racemization in short reaction times.

1-Hydroxy-2-phenylbenzimidazole (**8**) was synthesized as a white crystalline solid by coupling *ortho*-nitroaniline with benzyl bromide using sodium hydride as base, followed by benzyl deprotection using 10% Pd/C (Scheme 1).[17] The coupling reagents phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester (**9a**), diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester (**9b**) and phosphoric acid diphenyl ester 2-phenylbenzoimidazol-1-yl ester (**9c**) were synthesized by reaction of **8** with diethyl chlorophosphate, diphenylphosphorochloridate or diphenylphosphinic chloride, respectively, using triethylamine base in dichloromethane. The yields obtained for reagents **9a**, **9b** and **9c** were 67%, 71% and 63% respectively. To avoid the problem of unsatisfactory yield, a method was developed in which the reagents were synthesized and used in situ for the coupling reactions.

To standardize the reaction conditions for the coupling reactions, *N*-benzylbenzamide was synthesized by the reaction of benzoic acid with benzylamine using the coupling reagent **9a** in the presence of different solvents and bases. The results obtained (Table 1) showed that diisopropylethylamine (DIPEA) was the optimal base, in combination with dimethylformamide (DMF) as solvent.

Using the standardized reaction conditions, the scope of these reagents was examined through the synthesis of 27 different amides (Table 2), all of which were characterized by mass spectrometry and ^{1}H NMR spectroscopy. The use of these reagents proved to be superior to existing methods in respect to yield, reaction time and ease of purification. Coupling of carboxylic acids with sterically hindered amines such as isopropylamine and *tert*-butylamine also gave improved yields (Table 2, entries 22–

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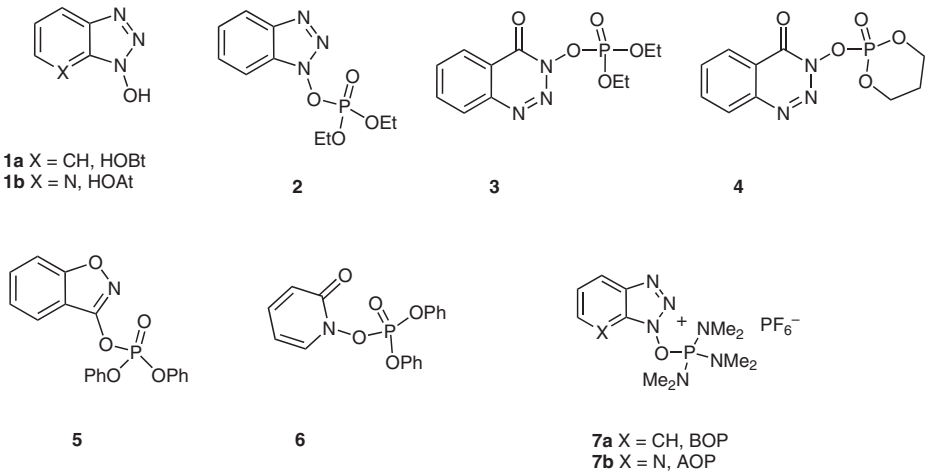
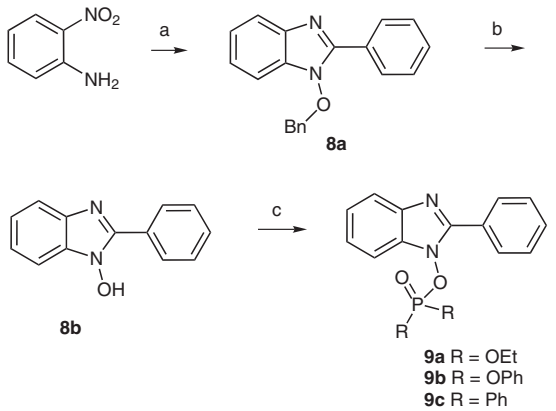


Figure 1 Some organophosphorus esters reported in the literature



Scheme 1 *Reagents and conditions*: (a) NaH, BnBr, 70 °C, 3 h; (b) H_2, Pd/C, MeOH, 15 min; (c) R_2POCl, Et_3N, CH_2Cl_2, 0 °C.

27).[18] The workup for these reactions was also simplified since acid-base treatment followed by trituration with an appropriate solvent (hexane or diethyl ether) directly gave the pure compound. Furthermore, the *N*-hydroxy-2-phenylbenzimidazole starting material could be recovered from the acidic aqueous extract and re-used for the synthesis of reagents.

As can be seen in Table 2, acids with electron-withdrawing substituents required less reaction time for coupling with amines (Table 2, entries 4, 5 and 6) as compared to acids with electron-donating substituents (Table 2, entries 10, 11 and 12). A comparative study of yields shows that reagents **9a** and **9b** gave slightly higher yields than **9c** (Table 2, *cf* entries 1, 2, 3 and 10, 11, 12). In some cases, however, reagent **9c** gave higher yields than either **9a** or **9b** (Table 2, entries 7, 8 and 9).

The applicability of **9a**, **9b** and **9c** as peptide coupling reagents was also examined. The reaction conditions were standardized with the coupling reaction of Cbz-Val-OH and Val-OMe·HCl using reagents **9a**, **9b** and **9c**. These results, together with those obtained by applying the optimized protocol to a range of other peptides, are summarized in Table 3. The yields obtained constitute an

Table 1 Synthesis of *N*-Benzylbenzamide: Effect of Solvent and Base on the Coupling Reagent **9a**

Solvent	Base	Time (h)	Yield (%)
MeCN	Et_3N	2.5	64
MeCN	DIPEA	2.5	53
DCM	Et_3N	2	71
DCM	DIEA	1.5	77
DMF	Et_3N	1	81
DMF	DIPEA	0.75	96
DMF	Lutidine	1.25	68
THF	Et_3N	3.5	57
THF	DIPEA	3	61

improvement on existing methods.[7a,18,19] In particular, the coupling of sterically hindered amino acids such as *tert*-butoxycarbonyl-protected α-aminoisobutyric acid (Boc-Aib-OH) with Val-OMe·HCl gave improved yields of 72%, 67% and 71% for reagents **9a**, **9b** and **9c**, respectively (Table 3, entries 10, 11 and 12).[19a] The extent of racemization (DL%) was examined by HPLC and found to be in the range of 0.4–2.7%, with the lowest being observed in the synthesis of the Cbz-Val-Val-OMe peptide using reagent **9b** (0.4%; Table 3, entry 2). The optical rotations of all the synthesized peptides were measured and found to be in agreement with those reported in the literature. Young's test[20] was performed for the coupling of Bz-Leu-OH and Gly-OEt·HCl (Table 3, entries 4, 5 and 6). In the case of reagent **9b** (Table 3, entry 5), this test revealed that only 1.6% racemization had taken place, which is significantly lower than reported methods using HOBt-based uronium salts [BOP (20%), PyBOP (15%) or HBTU (12.7%)].[21,22] Furthermore, Anteunis tests[23] showed that the coupling of Cbz-Gly-Phe-OH and Val-OMe·HCl (Table 3, entries 13, 14 and 15) gave diastereomeric ratios of 10:1, 10:1 and 9.05:0.5 for reagents **9a**, **9b** and **9c**, re-

Table 2 Synthesis of Amides Using Coupling Reagents **9a**, **9b** and **9c**

Entry	Acid	Amine	Amide	Reagent	Time (min)	Yield (%)
1	Benzoic acid (**10**)	Benzylamine (**11**)	*N*-Benzylbenzamide (**12**)	**9a**	45	96
2	**10**	**11**	**12**	**9b**	40	95
3	**10**	**11**	**12**	**9c**	45	91
4	4-Nitrobenzoic acid (**13**)	**11**	4-Nitro-*N*-benzylbenzamide (**14**)	**9a**	20	93
5	**13**	**11**	**14**	**9b**	20	91
6	**13**	**11**	**14**	**9c**	20	95
7	4-Bromobenzoic acid (**15**)	**11**	4-Bromo-*N*-benzylbenzamide (**16**)	**9a**	35	92
8	**15**	**11**	**16**	**9b**	35	92
9	**15**	**11**	**16**	**9c**	30	94
10	Anisic acid (**17**)	**11**	4-Methoxy-*N*-benzylbenzamide (**18**)	**9a**	55	97
11	**17**	**11**	**18**	**9b**	50	95
12	**17**	**11**	**18**	**9c**	55	88
13	Cinnamic acid (**19**)	**11**	*N*-Benzyl cinnamate (**20**)	**9a**	35	94
14	**19**	**11**	**20**	**9b**	35	91
15	**19**	**11**	**20**	**9c**	40	93
16	**10**	Cyclopropylamine (**21**)	*N*-Cyclopropylbenzamide (**22**)	**9a**	45	96
17	**10**	**21**	**22**	**9b**	30	96
18	**10**	**21**	**22**	**9c**	40	91
19	**10**	Piperidine (**23**)	Phenyl (piperidin-1-yl) methanone (**24**)	**9a**	30	95
20	**10**	**23**	**24**	**9b**	30	94
21	**10**	**23**	**24**	**9c**	30	94
22	**10**	Isopropylamine (**25**)	*N*-Isopropylbenzamide (**26**)	**9a**	45	91
23	**10**	**25**	**26**	**9b**	45	93
24	**10**	**25**	**26**	**9c**	50	88
25	**10**	*tert*-Butylamine (**27**)	*N*-*tert*-Butylbenzamide (**28**)	**9a**	70	90
26	**10**	**27**	**28**	**9b**	60	91
27	**10**	**27**	**28**	**9c**	60	84

spectively. These results were confirmed by HPLC, which showed 1.2, 0.9 and 1.7 DL percentages using the reagents **9a**, **9b** and **9c**, respectively. Considering the reaction times, yields and ease of workup, the application of these reagents thus constitutes an improved method for amide and peptide synthesis.

A comparative study of the three coupling reagents developed here, together with other commonly used systems, was performed on the coupling reaction of Z-Phg-OH with H-Pro-NH_2 in DMF, giving the peptide Z-Phg-Pro-NH_2 (**34**). The extent of racemization using coupling reagents *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) with additives such as HOBt, HOAt and HODht were found to be in the range of 3.3–24.6% (Table 4).[24] The reagents **9a**, **9b** and **9c** gave the desired compound in comparatively better yields and lower levels of racemization (1.1–2.4%).

During peptide coupling via uronium/guanidinium or phosphonium salts, the N-protected carboxylic acid first reacts with the coupling reagent to form an active ester, which subsequently reacts with the amino component to give the corresponding amide. Regarding the coupling reagents developed here, when the reagents **9a**, **9b** and **9c** were reacted with the appropriate acid (benzoic acid/Cbz-Val-OH) in cooled DMF, using diisopropylethylamine as base for 10 min (Scheme 2), the active esters (**35** for ben-

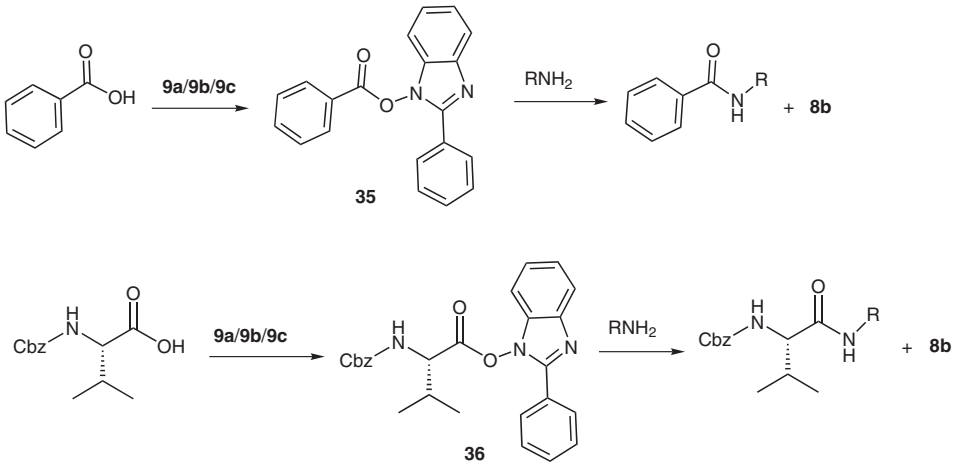
Table 3 Synthesis of Peptides Using Reagents **9a–c**

Entry	Peptide product	Reagent	Time (h)	Yield[a] (%)	Racemization[b] (DL%)	$[\alpha]_D^{25}$ (*c*, solvent)
1	Cbz-Val-Val-OMe (**29**)	**9a**	3	89	1.1	–28.7 (1, EtOH)[c]
2	**29**	**9b**	3	92	0.4	–26.2 (1, EtOH)[c]
3	**29**	**9c**	2.5	91	0.7	–26.8 (1, EtOH)[c]
4	Bz-Leu-Gly-OEt (**30**)	**9a**	3	85	1.8	–32.3 (3.1, EtOH)[d]
5	**30**	**9b**	3.5	78	1.6	–33.8 (3.1, EtOH)[d]
6	**30**	**9c**	3.5	84	2.7	–31.2 (3.1, EtOH)[d]
7	Cbz-Leu-Gly-OEt (**31**)	**9a**	2.5	81	2.1	–19.8 (1, EtOH)
8	**31**	**9b**	3	67	0.8	–20.4 (1,EtOH)
9	**31**	**9c**	3	74	1.9	–21.1 (1,EtOH)
10	Boc-Aib-Val-OMe (**32**)	**9a**	4	72	–	+21.7 (1, EtOH)[e]
11	**32**	**9b**	4	67	–	+20.4 (1, EtOH)[e]
12	**32**	**9c**	4	71	–	+20.9 (1, EtOH)[e]
13	Cbz-Gly-Phe-Val-OMe (**33**)[f]	**9a**	3.5	76	1.2	+15.8 (1, EtOH)
14	**33**[f]	**9b**	3.5	72	0.9	+15.2 (1, EtOH)
15	**33**[f]	**9c**	3.5	69	1.7	+16.4 (1, EtOH)

[a] Isolated yields, based upon the starting amino acid, after column chromatography.
[b] DL% equal to % of D-isomer multiplied by two.
[c] Lit.[8b] $[\alpha]_D^{20}$ –28 (*c* 1, EtOH).
[d] Lit.[19] $[\alpha]_D^{20}$ –34 (*c* 3.1, EtOH). Young's test; epimerization: 2.7% (entry 4), 1.6% (entry 5), 4.6% (entry 6).
[e] Lit.[23] $[\alpha]_D^{20}$ –19.5 (*c* 1, EtOH).
[f] Anteunis test[23] (^{1}H NMR, 400 MHz); diastereomeric ratios: 10:1 (entries 13 and 14), 9.5:0.5 (entry 15).

zoic acid and **36** for Cbz-Val-OH) could be isolated and characterized by mass and ^{1}H NMR. These results indicate that the reaction pathway for these reagents should be similar to those of the organophoshorus derivatives of HOBt and HOAt.

In conclusion, phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester (**9a**), diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester (**9b**) and phosphoric acid diphenyl ester 2-phenylbenzimidazol-1-yl ester (**9c**) have been easily prepared from *N*-hydroxy-2-phenylbenzimidazole and used in situ for coupling reactions to synthesize amides and peptides. The advantages of these peptide coupling reagents are their scalability, minimal levels of racemization, higher yields and use of readily available, inexpensive starting materials for the synthesis of reagents. Another promising feature of these reagents is



Scheme 2 Isolation of active ester intermediates **35** and **36**

that, after completion of coupling reaction, the by-product *N*-hydroxy-2-phenyl benzimidazole could be easily separated by acid-base treatment and re-used for the synthesis of reagents **9a**, **9b** and **9c**. Furthermore, these reagents give improved yields for coupling of sterically hindered amino acids such as aminoisobutyric acid with acid-protected amines. In summary, the reagents **9a**, **9b** and **9c** have been found to be versatile reagents for the synthesis of amides and peptides, which complement and extend previously reported methods.

Table 4 Effect of Coupling Reagents on the Yield and Extent of Racemization in the Synthesis of Z-Phg-Pro-NH_2 (**34**) in DMF[24]

Coupling reagents	Yield (%)	DL%
DCC/HOBt	89.2	9.3
EDC/HOBt	81.9	10.1
DCC/HOAt	83	3.3
EDC/HOAt	81.4	7.0
DCC/HODht	89.2	16.7
EDC/HODht	80.4	24.6
9a	91	1.7
9b	88	1.1
9c	93	2.4

The amino acid derivatives were obtained from commercial sources or synthesized according to the literature. Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Varian Gemini spectrometer and are reported as parts per million (ppm) downfield from TMS internal standard. Mass spectra were taken with Micromass - QUATTRO-II of WATER mass spectrometer. The optical rotations were determined using a Rudolph degipole automatic polarimeter. HPLC was performed using a Zorbax SB-C18 reverse phase column (0.46 × 25 cm) on Shimadzu instrument equipped with an automatic injector and a UV-PDA detector (215 nm). The mobile phase consisted of 0.05% TFA and MeCN–H_2O (1:1). The products were eluted isocratically at a flow rate of 1 mL/min. Flash column chromatography was performed with 300–400 mesh silica gel and analytical TLC was performed on precoated silica gel plates ($60F_{254}$) with the elution systems indicated. Solvents and reagents were purified by standard methods as necessary. Amino acids are of the L-configuration if not otherwise mentioned.

N-Hydroxybenzyl-2-phenylbenzimidazole (8a)

NaH (1.94 g, 0.048 mol) was suspended in THF (30 mL) and *o*-nitroaniline (2.68 g, 0.02 mol) was added portion-wise with cooling. After 15 min, benzyl bromide (5.8 g, 0.05 mol) was added slowly and the mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to r.t., quenched with H_2O (25 mL) and extracted into EtOAc (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The product was isolated by trituration with hexane and filtration. Off-white solid; yield: 5.67 g (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.1 (s, 2 H), 7.2–7.4 (m, 5 H), 7.6–7.8 (m, 5 H), 7.8 (d, *J* = 8.2 Hz, 2 H), 8.2 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 301 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.03; H, 5.41; N, 9.31.

N-Hydroxy-2-phenylbenzimidazole (8b)

N-Hydroxybenzyl-2-phenylbenzimidazole (**8a**; 5.2 g 0.17 mol) was dissolved in MeOH (50 mL), Pd/C (10%, 500 mg) was added and the mixture was stirred under a H_2 atmosphere at r.t. for 15 min. The reaction mixture was filtered through high-flow celite and the filtrate was concentrated and purified by column chromatography (10% MeOH–$CHCl_3$) to yield the title compound as a white solid. Yield: 3.55 g (98%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.2–7.4 (m, 2 H), 7.6–7.8 (m, 5 H), 8.2 (d, *J* = 8.3 Hz, 2 H), 12.2 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 211 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 73.82; H, 4.71; N, 13.29.

1-[(Diethoxyphosphoryl)oxy]-2-phenyl-1*H*-benzimidazole (9a); Typical Procedure

A solution of *N*-hydroxy-2-phenylbenzimidazole (**8b**; 0.420 g, 0.02 mol) and Et_3N (0.695 mL, 0.05 mol) was stirred in CH_2Cl_2 (2.5 mL) and diethyl chlorophosphate (0.212 mL, 0.024 mol) was added at 0 °C. The mixture was stirred until the reaction was complete (monitored by TLC) then the solvent was evaporated and the residue was stirred with pentane (20 mL) and decanted. The remaining residue was stirred with Et_2O (2 × 15 mL) and decanted three times. The combined Et_2O extracts were concentrated to yield the title compound.

Yield: 462 mg (67%); colorless solid; mp 112–116 °C (dec).

IR (Nujol): 2985, 1298, 1036, 981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.2 (t, *J* = 6.2 Hz, 6 H) 4.1 (q, *J* = 7.4 Hz, 4 H), 7.3 (m, *J* = 8.1 Hz, 3 H), 7.5 (d, *J* = 8.1 Hz, 2 H), 7.8 (d, *J* = 8.2 Hz, 2 H), 8.2 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 347 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{19}N_2O_4P$: C, 58.96; H, 5.53; N, 8.06. Found: C, 59.13; H, 5.59; N, 8.11.

1-[(Diphenoxyphosphoryl)oxy]-2-phenyl-1*H*-benzimidazole (9b)

Yield: 624 mg (71%); white solid; mp 93–95 °C (dec).

IR (Nujol): 2930, 1244, 1105, 1018 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.4 (m, 13 H), 7.6 (d, *J* = 8.0 Hz, 2 H), 7.8 (d, *J* = 8.2 Hz, 2 H), 8.2 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 443 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{19}N_2O_4P$: C, 67.87; H, 4.33; N, 6.33. Found: C, 67.81; H, 4.41; N, 6.30.

1-[(Diphenylphosphoryl)oxy]-2-phenyl-1*H*-benzimidazole (9c)

Yield: 516 mg (63%); white solid; mp 131–133 °C (dec).

IR (Nujol): 3016, 1165, 1045, 993 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.1–7.4 (m, 13 H) 7.6 (d, *J* = 8.1 Hz, 2 H), 7.7 (d, *J* = 8.2 Hz, 2 H), 8.2 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 411 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{19}N_2O_2P$: C, 73.16; H, 4.67; N, 6.83. Found: C, 72.78; H, 4.71; N, 6.86.

Synthesis of Amides and Peptides; General Procedure

A solution of *N*-hydroxy-2-phenylbenzimidazole (**8b**; 420 g, 0.02 mol) and DIPEA (0.83 mL, 0.05 mol) was stirred in DMF (2.5 mL) and diethyl chlorophosphate (0.212 mL, 0.024 mol) was added with cooling. The reaction mixture was stirred for 10 min then the acid

component (0.016 mol) was added and the reaction was stirred for a further 10 min at 0 °C. The amine component (0.03 mol) was added and the mixture was stirred at r.t. until the reaction was complete (monitored by TLC). Sat. aq NaCl (20 mL) was added and the mixture was extracted with EtOAc (2 × 15 mL). The organic layer was washed with HCl (2 N, 15 mL), sat. aq $NaHCO_3$ (15 mL) and H_2O (2 × 20 mL), dried (Na_2SO_4) and the solvent removed to give the corresponding amide or peptide.

_N_-Benzylbenzamide (12)
White solid; mp 104–106 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.8 (d, *J* = 5.6 Hz, 2 H), 6.4 (br s, 1 H), 7.35–7.6 (m, 8 H), 7.8 (d, *J* = 8.1 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 212 [M + H]$^+$.

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 78.93; H, 6.23; N, 6.58.

4-Nitro-_N_-benzylbenzamide (14)
Off-white solid; mp 138–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.6 (d,*J* = 5.9 Hz, 2 H), 6.55 (s, 1 H), 7.35 (m, 5 H), 7.7 (d, *J* = 6.8 Hz, 2 H), 8.3 (d, *J* = 6.8 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 257 [M + H]$^+$.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.48; H, 4.68; N, 10.91.

4-Bromo-_N_-benzylbenzamide (16)
White solid; mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.6 (d, *J* = 5.5 Hz, 2 H), 6.45 (s, 1 H), 7.28 (m, 5 H), 7.55 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.1 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 291 [M + H]$^+$.

Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; N, 4.83. Found: C, 58.37; H, 4.21; N, 4.89.

4-Methoxy-_N_-benzylbenzamide (18)
White solid; mp 128–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.8 (s, 3 H), 4.62 (d, *J* = 5.6 Hz, 2 H), 6.38 (s, 1 H), 6.9 (d, *J* = 8.2 Hz, 2 H), 7.32 (m, 5 H), 7.78 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 242 [M + H]$^+$.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 76.67; H, 6.27; N, 5.80. Found: C, 76.61; H, 6.23; N, 5.81.

_N_-Benzyl Cinnamate (20)
White solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.55 (d, *J* = 5.2 Hz, 2 H), 5.9 (s, 1 H), 6.4 (d, *J* = 8.2 Hz, 1 H), 7.4 (m, 5 H), 7.8 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 238 [M + H]$^+$.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.12; H, 6.39; N, 6.02.

_N_-Cyclopropylbenzamide (22)
White solid; mp 153–154 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (dd, *J* = 3.7 Hz, 2 H), 0.85 (dd, *J* = 3.7, 5.2 Hz, 2 H), 2.8 (m, 1 H), 7.3 (m, 3 H), 7.8 (d, *J* = 5.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 146 [M + H]$^+$.

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.53; H, 6.93; N, 8.67.

Phenyl (Piperidin-1-yl) Methanone (24)
White solid; mp 167–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.30 (m, 3 H), 1.40 (m, 2 H), 1.62 (m, 1 H), 2.0 (dd, *J* = 7.1, 5.4 Hz, 2 H), 4.0 (m, 1 H), 7.4 (m, 3 H), 7.8 (d, *J* = 8.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 190 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.21; H, 8.04; N, 7.39.

_N_-Isopropylbenzamide (26)
White solid; mp 137–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 3.6 Hz, 6 H), 4.3 (m, 1 H), 6.0 (s, 1 H), 7.4 (m, 3 H), 7.7 (d, *J* = 6.8 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 164 [M + H]$^+$.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.61; H, 8.11; N, 8.57.

N-tert-Butylbenzamide (28)
White solid; mp 151–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (s, 9 H), 6.0 (s, 1 H), 7.4 (m, 3 H), 7.7 (d, *J* = 5.9 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 178 [M + H]$^+$.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 7.90; N, 9.03. Found: C, 75.26; H, 7.94; N, 9.02.

Cbz-Val-Val-OMe (29)
White solid; mp 110–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 12 H), 2.04–2.19 (m, 2 H), 3.73 (s, 3 H), 4.0–4.10 (m, 1 H), 4.55 (dd, *J* = 8.5, 4.9 Hz, 1 H), 5.12 (s, 2 H), 5.41 (d, *J* = 8.5 Hz, 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 7.34 (m, 5 H).

MS (EI, 70 eV): *m*/*z* = 365 [M + H]$^+$.

Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.65; H, 7.79; N, 7.67.

Bz-Leu-Gly-OEt (30)
White solid; mp 150–151 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9 (d, *J* = 6.2 Hz, 6 H), 1.25 (t, *J* = 7.3 Hz, 3 H), 1.58–1.6 (m, 1 H), 1.7 (m, 2 H), 4.0 (d, *J* = 5.8 Hz, 2 H), 4.25 (q, *J* = 7.3 Hz, 2 H), 5.1 (s, 1 H), 5.5 (br s, 1 H), 7.25 (m, 5 H).

MS (EI, 70 eV): *m*/*z* = 321 [M + H]$^+$.

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 62.01; H, 7.61; N, 8.67.

Cbz-Leu-Gly-OEt (31)
White solid; mp 141–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9 (d, *J* = 6.1 Hz, 6 H), 1.25 (t, *J* = 7.3 Hz, 3 H), 1.58–1.6 (m, 1 H), 1.7 (m, 2 H), 4.0 (d, *J* = 7.6 Hz, 2 H), 4.25 (q, *J* = 7.6 Hz, 2 H), 5.12 (m, 2 H), 5.5 (br s, 1 H), 7.25 (m, 5 H).

MS (EI, 70 eV): *m*/*z* = 351 [M + H]$^+$.

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 60.89; H, 7.51; N, 8.02.

Boc-Aib-Val-OMe (32)
White solid; mp 111–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.92 (2 × d, *J* = 7.0 Hz, 6 H), 1.44–1.52 (3 × s, 15 H), 2.16 (m, 1 H), 3.73 (s, 3 H), 4.52 (dd, *J* = 8.5, 4.9 Hz, 1 H), 4.93, 7.20 (2 × br s, 2 H).

MS (EI, 70 eV): *m*/*z* = 351 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 57.31; H, 8.96; N, 8.67.

Cbz-Gly-Phe-Val-OMe (33)
White solid; mp 123–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (2 × d, *J* = 7.0 Hz, 6 H), 1.95 (m, 1 H), 2.94 (m, 2 H), 3.57 (s, 3 H), 4.34 (dd, *J* = 8.0, 5.5 Hz, 1 H), 5.01 (s, 2 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.04–7.26 (m, 10 H).

MS (EI, 70 eV): *m*/*z* = 399 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.06. Found: C, 65.71; H, 6.61; N, 7.08.

Cbz-Phg-Pro-NH_2 (34)
White solid; mp 89–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.1–2.2 (m, 4 H), 3.2 (m, 1 H), 3.7 (m, 1 H), 4.65 (m, 1 H), 5.13 (s, 2 H), 5.6 (m, 2 H), 6.25 (m, 1 H), 6.65 (m, 1 H), 7.25–7.6 (m, 10 H).

MS (EI, 70 eV): *m*/*z* = 382 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.14; H, 6.04; N, 11.02. Found: C, 66.21; H, 6.08; N, 10.86.

2-Phenyl-1-[(phenylcarbonyl)oxy]-1*H*-benzimidazole (35)
Off-white solid; mp 234–235 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2 (m, 2 H), 7.4 (m, 3 H), 7.5–7.7 (m, 7 H), 8.2 (d, *J* = 7.8 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 315 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 77.02; H, 4.56; N, 8.90.

2-Phenyl-1*H*-benzimidazol-1-yl *N*-[(Benzyloxy)carbonyl]-l-valinate (36)
White solid; mp 163–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.5 Hz, 6 H), 2.2 (m, 1 H), 4.1 (m, 1 H), 4.8 (s, 1 H), 5.41 (s, 2 H), 7.15–7.30 (m, 7 H), 7.5–7.7 (m, 5 H), 8.2 (d, *J* = 8.4 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* = 444 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{25}N_3O_4$: C, 70.41; H, 5.68; N, 9.47. Found: C, 69.86; H, 5.62; N, 9.52.

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