Peptide Bond Formation Using Polymer-Bound BOP

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A new polymer-supported BOP (**P**-BOP) has been prepared starting from the commercially available polystyrene-bound 1-hydroxybenzotriazole (**P**-HOBt) and successfully used as a solid-supported reagent for peptide-coupling reactions. Compared to BOP, less epimerization was observed. **P**-BOP is also a suitable activating reagent for difficult peptide coupling reactions involving α,α-dialkyl amino acids.

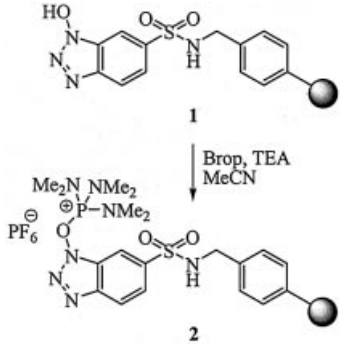
Introduction

In recent years, the benefits of performing organic synthesis using polymer-supported reagents have been fully recognized. One major advantage lies in the fact that workup procedures are simplified. Moreover, combination of benefits of polymer-supported reactions with those of solution-phase chemistry (e.g., easy monitoring of the reaction progress by simply applying LC-MS or TLC techniques) made polymer-supported reagents a widespread appreciated alternative. Peptide synthesis also takes the advantage of the emerging supported reagents technology, especially in those aspects regarding the formation of amide bonds. Carbodiimide (**P**-EDC),[1] 1-hydroxybenzotriazole (**P**-HOBt)[2,3] and 4-(dimethylamino)pyridine (**P**-DMAP)[4] supported on normal cross-linked polystyrene beads or on macroporous polystyrene were used as activating agents, **P**-HOBt and **P**-DMAP requiring the presence of an activating reagent like PyBrop (bromotrispyrrolidinophosphonium hexafluorophosphate) or DCC (dicyclohexylcarbodiimide). Recently, the synthesis of polymeric *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (**P**-TBTU)[5] was reported. **P**-TBTU allows direct formation of the amide bond and recovery of immobilized HOBt by filtration once the reaction is complete.

(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) has been described as an activation reagent ideally suited for solid phase peptide synthesis and the rate of coupling compares favorably to other methods of activation.[6,7] BOP has also proved to be very efficient for the difficult coupling of α,α-dialkyl amino acids (e.g. Aib).[8] In connection with our research directed towards the development of new methodologies for automated synthesis of peptides, we wish to report the synthesis of a new polymer-supported peptide coupling reagent **P**-BOP (**2**)[9] and its use in model peptide couplings.

Results and Discussion

P-BOP (**2**) was prepared by the reaction of commercially available **P**-HOBt (**1**) (1 mmol/g resin loading) with 5 equiv. of bromotris(dimethylamino)phosphonium hexafluorophosphate (Brop), at room temperature for 18 h, in the presence of triethylamine (TEA) as base and in acetonitrile as solvent (Scheme 1).



Scheme 1. Synthesis of **P**-BOP (**2**)

The reaction progress between **P**-HOBt (**1**) and Brop was monitored by IR spectroscopy and was considered to be complete after the disappearance of the broad O−H stretching band of **P**-HOBt at $\tilde{\nu} = 3314\ cm^{-1}$. The resulting polymer **2** was filtered, washed successively with acetonitrile, methanol, dichloromethane and diethyl ether, and

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dried at 50 °C in vacuo (6 mbar). IR spectra of the resulting resin displayed three new strong bands at $\tilde{\nu}$ = 843 (assigned to P−F) and 1064 and 1320 cm^{-1} (both corresponding to P−NMe_2) (Figure 1).

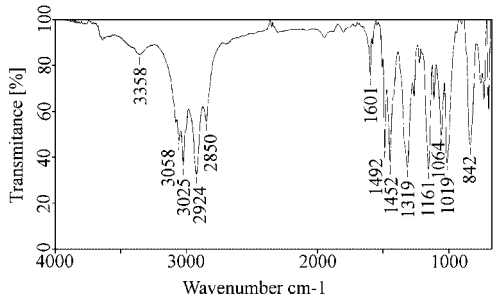
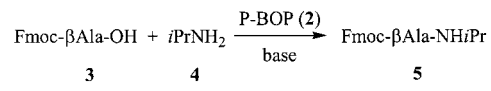


Figure 1. The IR spectra of **P**-BOP (**2**)

Gel-phase ^1H NMR of the resin in CD_2Cl_2 as solvent, showed the appearance of a broad single peak at δ = 2.90 ppm, which was attributed to the N−Me groups. Elemental analysis of both **P**-HOBt (**1**) and **P**-BOP (**2**) showed a molecular ratio N/S of 3.98:1 for resin **1**, while for **2** the molecular ratio N/S was 6.78:1. These values are in agreement with the structural formula of both polymer-supported reagents and clearly show an increase in nitrogen content for **P**-BOP (**2**) compared to the starting **P**-HOBt (**1**). Based on these values, the loading of the resin can be calculated at 0.91 mmol/g. However, the effective resin loading was determined based on the synthesis of Fmoc-βAla-NH*i*Pr (**5**) since part of the functionality might not be accessible. (Scheme 2).



Scheme 2. Reaction used for determination of the effective resin loading of **P**-BOP (**2**)

For the coupling reaction between **3** and **4**, a theoretical value of 1 mmol/g resin loading was used for **P**-BOP (**2**), by virtually considering the total conversion of the **P**-HOBt (**1**). In a standard procedure, to a suspension of 1 equiv. of **P**-BOP (**2**) (50 mg) in 3 mL of the corresponding solvent, 2 equiv. of Fmoc-βAla-OH (**3**) was added, followed by 2 equiv. of organic base, namely pyridine or TEA. The mixture was shaken at room temperature for 15 min, then isopropylamine (**4**) was added and the shaking continued for 16 h. After filtration, the resin was subsequently washed with acetonitrile and dichloromethane (DCM), and the solvents were removed in vacuo. The resulting crude reaction mixture was dissolved in acetonitrile and methanol, and submitted to the HPLC analysis. The chromatogram was recorded at 263 nm (Figure 2, C) and the effective resin loading was calculated using the following formula: Loading [mmol/g] = $(A_1 \times n)/[(A_1 + A_2) \times q]$; n = mmol of Fmoc-βAla-OH; q = mg of **P**-BOP (**2**) resin; A_1 = peak area of Fmoc-βAla-NH*i*Pr (9.12 min) at 263 nm; A_2 = peak area of unchanged Fmoc-βAla-OH (8.75 min) at 263 nm.

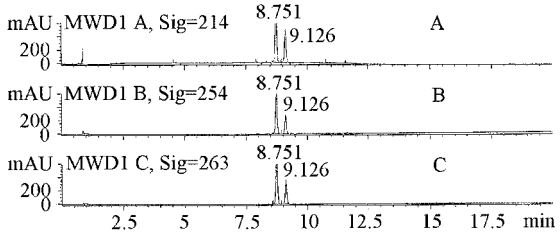


Figure 2. The HPLC chromatogram of the crude reaction mixture resulting after the coupling between **3** and **4**, in dichloromethane and using pyridine as base, at λ = 214 (A), 254 (B) and 263 nm (C), respectively

Reaction of Fmoc-βAla-OH (**3**) with isopropylamine (**4**) showed to be solvent-dependent and slightly influenced by the nature of the base, i.e. pyridine or TEA (Table 1). HPLC analysis of the crude reaction mixture showed that the Fmoc protecting group was stable under the reaction conditions, since no side-product absorbing at λ = 254 nm was detected by HPLC (Figure 2, B). The effective resin loading was found to be around 0.6−0.7 mmol/g, depending on the nature (and the dryness) of the solvent, which suggested that not all polymer-bound BOP (**2**) was available for coupling or that a part of it was destroyed by the water of the solvent (Table 1).

Table 1. Variation of the effective resin loading of **P**-BOP (**2**) according to the nature of the solvent and base

Entry	Solvent	Base [0.033 M]	Loading [mmol/g]
1	MeCN	pyridine	0.61
2	MeCN	TEA	0.60
3	DCM	pyridine	0.76
4	DCM	TEA	0.72

Starting from *N*-protected amino acids and amino acid ester hydrochlorides, a series of dipeptides was prepared using **P**-BOP (**2**) as solid-supported coupling reagent (Table 2) in the presence of an organic base. Acetonitrile and dichloromethane were tested as solvents and a better resin swelling was observed for DCM. Pyridine and TEA were tested as bases (Table 2, Entries 1−4), the latter affording higher yields. In a standard procedure, as detailed in the Exp. Sect., to a suspension of **P**-BOP in the corresponding solvent, the *N*-protected amino acid was added, followed by the amino ester hydrochloride and the organic base, namely pyridine, TEA or DIPEA.

The yields of isolated peptides were good and the levels of epimerization in Young's and Anteunis's tests (Table 2, Entries 5 and 6) were similar to those reported in the literature for other polymer-supported peptide coupling reagents.[5] A more hindered base such as *N*,*N*′-diisopropylethylamine (DIPEA) was used in place of pyridine or TEA to minimize racemization. Chiral HPLC analysis of the di-

Table 2. Peptides prepared using **P**-BOP (**2**) as coupling reagent

Entry	Peptide[a]	Solvent	Base	Yield [%][b]
1	BocGly-PheOEt (**6**)	MeCN	TEA	74
2	BocGly-PheOEt (**6**)	MeCN	pyridine	68
3	BocGly-PheOEt (**6**)	DCM	TEA	80
4	BocGly-PheOEt (**6**)	DCM	pyridine	78
5	BzLeu-GlyOEt (**7**)[c]	DCM	DIPEA	82
6	ZGlyPhe-ValOMe (**8**)[d]	DCM/MeCN (1:1)	DIPEA	80
7	BocAib-PheOEt (**9**)	DCM	TEA	75
8	BocAib-ValOMe (**10**)	DCM	TEA	76

[a] The reactions were performed at room temp. for 18 h. [b] Isolated pure peptides. [c] Young's test: *ee* = 53%. [d] Anteunis's test: no detectable epimerization (^{1}H NMR, 400 MHz).

peptide generated by coupling Bz-L-Leu-OH and H-Gly-OEt (Young's test), showed 23.5% of the D-isomer, whereas unsupported BOP reagent is reported to induce 60% racemization when the mentioned test is carried out.[10] Similar to **P**-TBTU,[5] no epimerization was detected in the tripeptide generated by coupling Z-Gly-Phe-OH and H-Val-OMe (Anteunis's test) as shown by ^{1}H NMR analysis (400 MHz). Contrary to the results reported with the polymer-supported TBTU reagent,[5] heating was not required and Z-Gly-Phe-Val-OMe was obtained in higher yield using **P**-BOP (**2**). Moreover, good yields were obtained for the difficult couplings involving the sterically hindered Aib (Table 2, Entries 7 and 8), showing that **P**-BOP (**2**) preserves this very important property of the BOP reagent.

Conclusions

In conclusion, **P**-BOP (**2**) is a promising new polymer-supported peptide coupling reagent, inducing an acceptable degree of epimerization during synthesis of standard peptides. Moreover, these preliminary results indicate that **P**-BOP (**2**) is also a suitable activating reagent for difficult peptide coupling reactions involving α,α-dialkyl amino acids.

Experimental Section

General Remarks: All reactions were carried out in 10-mL polypropylene reactors (MultiSynTech GMBH). All commercial reagents and solvents were used without further purification. The polymer-supported HOBt [PS-HOBt(HL), 1.0 mmol/g] was purchased from Argonaut Technologies. The Brop was purchased from Fluka. HPLC analyses were performed using a 4.6 × 50 mm reversed phase Waters Symmetry Shield RP_{18} 5μm column, with a Hewlett−Packard 1050 HPLC system. A gradient starting from 100%H_2O/0.1%TFA up to 100%MeCN/0.1%TFA within 14 min at 1 mL/min flow rate was used. The chiral HPLC analyses were performed using a 4.6 × 150 mm Chiracel OD-R 5μm column, under isocratic conditions (0.5 M $NaClO_4$/MeCN, 60:40) and UV detection at 214 nm, with a Hewlett−Packard 1050 HPLC system. The LC-MS analyses were performed using a 2.1 × 50 mm reversed phase Intercom C18 3μm column, with a Hewlett−Packard 1100 LC system coupled with a MS Micromass Platform LC mass analyser, operating at 3.5 kV. A gradient starting from 90%H_2O/10%MeCN up to 10%H_2O/90%MeCN within 15 min at 0.2 mL/min flow rate was used. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX250 spectrometer at 250 MHz, respectively 63 MHz. Gel-phase ^{1}H NMR spectra were recorded with a Bruker Avance spectrometer at 400 MHz, equipped with an HRMAS probehead. Chemical shifts δ are given in ppm relative to TMS; coupling constants *J* are reported in Hz. IR spectra were recorded using a Bruker Vector 22 spectrometer coupled with a microscope. Elemental analyses were determined by Service Central d'Analyse, CNRS, Vernaison, France. Analytical TLC plates (Silica gel 60 F_{254} on glass) were purchased from Merck. Silica gel 60 (40−63 μm, Merck) was used for flash chromatography.

Synthesis of P-BOP (2): Brop (1.94 g, 5 mmol, 5 equiv.) was added to a suspension of **P**-HOBt (1 mmol/g, 1.0 g, 1 mmol, 1 equiv.) in MeCN (5 mL), followed by addition of TEA (0.5 g, 0.7 mL, 5 mmol, 5 equiv.). The suspension was shaken at room temperature for 18 h. At this time the polymer was filtered, washed with MeCN (4 × 10 mL), MeOH (2 × 10 mL), DCM (4 × 10 mL), dry Et_2O (4 × 10 mL), and dried at 50 °C in vacuo (6 mbar), to furnish a light-brown resin. IR (resin bead deposited on NaCl window): $\tilde{\nu}$ = 3358 (NH), 3058, 3025, 2924, 2850, 1601, 1492, 1452, 1319 (P−NMe_2), 1161 (SO_2−N), 1064 (P−NMe_2), 1019, 842 (P−F) cm^{-1}. ^{1}H NMR (400 MHz, CD_2Cl_2, gel phase): δ = 6.20−7.50 (br., aromatic), 2.90 (br. $PN(CH_3)_2$], 2.60−2.80 (m, CH_2) ppm. Elemental analysis: found C 62.68, H 6.50, N 8.84, P 3.90, S 2.98.

General Procedure for the Determination of the Effective Loading of P-BOP (2): Fmoc-βAla-OH (31.2 mg, 0.1 mmol, 2 equiv.) was added to suspension of **P**-BOP (theoretical loading 1 mmol/g, 50 mg, 0.05 mmol, 1 equiv.) in the corresponding solvent (3 mL), followed by the organic base (0.1 mmol, 2 equiv.). The mixture was shaken at room temperature for 15 min, then *i*$PrNH_2$ (6.5 mg, 9.42 μL, 0.011 mmol, 2.2 equiv.) was added and the shaking continued for 16 h. At this time the polymer was filtered and washed with MeCN (5 mL) and DCM (5 mL). The filtrate and the washings were combined, and the solvents were removed by evaporation. The crude reaction mixture was dissolved in MeCN (10 mL) and MeOH (3 mL), and submitted to the HPLC analysis.

General Procedure for Peptide Coupling Using P-BOP (2): The *N*-protected amino acid (0.15 mmol, 1 equiv.) was added to a suspension of **P**-BOP (0.76 mmol/g, 0.30 g, 0.23 mmol, 1.5 equiv.) in the corresponding solvent (3 mL), followed by the amino ester hydrochloride (0.18 mmol, 1.2 equiv.) and the base (0.60 mmol, 4 equiv.). The mixture was shaken at room temperature for 18 h, the resin was filtered and washed with DCM (3 × 5 mL). After evaporation of the solvent, the crude reaction mixture was dissolved in EtOAc, washed with $NaHCO_3$ saturated aqueous solution (3 × 15 mL), $KHSO_4$ saturated aqueous solution (3 × 15 mL) and dried with

$MgSO_4$. The resulting oil showed to be pure by TLC. However, a sample was purified by flash chromatography on silica gel (DCM/MeOH, 8:1) for analytical purposes.

Boc-Gly-Phe-OEt (6):[3] Light-yellow oil. Yield 68−80% (see Table 2). R_f = 0.57 (DCM/MeOH, 8:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH$_2$), 1.33 (s, 9 H, *t*Bu), 3.05 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2Ph), 3.67−3.78 (m, 2 H, NHCH_2), 4.10 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH$_3$CH_2), 4.79 (m, 1 H, C*H*-Bn), 5.04 (br. s, 1 H, N*H*), 6.42 (br. s, 1 H, N*H*), 7.05−7.28 (m, 5 H, ArH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.0 (CH_3), 27.2 (*t*Bu), 36.9 (CH_2-*Phe*), 44.0 (CH_2-*Gly*), 52.0 (CH-*Phe*), 60.5 (CH_2), 79.5 (C), 126.1 (Ar), 127.5 (Ar), 128.2 (Ar), 134.6 (Ar), 167.8 (C=O), 167.9 (C=O), 170.2 (C=O) ppm.

Bz-Leu-Gly-OEt (7):[11] White solid. Yield 82% (63 mg). R_f = 0.51 (DCM/MeOH, 8:1). t_R (chiral HPLC) = 13.32 (major), 14.79 (minor) min. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 [d, $^3J_{H,H}$ = 6.1 Hz, 6 H, (CH_3)$_2$CH], 1.20 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH$_2$), 1.58−1.80 (m, 3 H, CH_2CH, (CH$_3$)$_2$C*H*], 3.90−4.02 (m, 2 H, CH_2NH), 4.10 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH$_3$CH_2), 4.74 (m, 1 H, C*H*NH), 5.60 (br. s, 1 H, N*H*), 6.70 (br. s, 1 H, N*H*), 7.30−7.81 (m, 5 H, ArH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.0 (CH_3-*Leu*), 22.0 (CH_3-*Leu*), 24.7 (CH-*Leu*), 41.0 (CH_2-*Leu*), 41.2 (CH_2-*Gly*), 51.8 (NHCH-*Leu*), 61.3 (CH_2), 127.0 (Ar), 128.4 (Ar), 131.6 (Ar), 133.5 (Ar), 167.4 (C=O), 169.4 (C=O), 172.5 (C=O) ppm. LC-MS: *m*/*z* = 321 [M + H]$^+$.

Z-Gly-Phe-Val-OMe (8):[12] White solid. Yield 80% (94 mg). R_f = 0.62 (DCM/MeOH, 8:1). t_R (HPLC) = 7.62 (minor), 8.65 (major) min. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.71 [d, $^3J_{H,H}$ = 7.1 Hz, 3 H, (CH_3)$_2$CH], 0.79 [d, $^3J_{H,H}$ = 7.1 Hz, 3 H, (CH_3)$_2$CH], 1.99 [m, 1 H, C*H*(CH$_3$)$_2$], 2.99 (m, 2 H, CH_2Ph), 3.62 (s, 3 H, CH$_3$O), 3.79 (d, $^3J_{H,NH}$ = 5.4 Hz, 2 H, HNCH_2CO), 4.35 (dd, $^3J_{H,H}$ = 8, $^3J_{H,NH}$ = 5 Hz, 1 H, HNC*H*-*i*Pr), 4.64 (m, 1 H, C*H*-Bn), 5.04 (s, 2 H, CH_2OCONH), 5.33 (br., 1 H, N*H*CH$_2$), 6.25 (d, $^3J_{H,NH}$ = 7.2 Hz, 1 H, N*H*CH-Bn), 6.63 (d, $^3J_{H,NH}$ = 7.2 Hz, 1 H, N*H*CH-*i*Pr), 7.10−7.35 (m, 10 H, ArH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.6 (CH_3-*Val*), 18.7 (CH_3-*Val*), 20.6 (CH-*Val*), 38.3 (CH_2-*Phe*), 44.1 (CH_2-*Gly*), 52.0 (OCH_3), 54.4 (CH-*Phe*), 57.3 (NHCH-*Val*), 66.9 (OCH_2), 126.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 129.2 (Ar), 136.1 (Ar), 156.5 (Ar), 169.3 (C=O), 171.2 (C=O), 171.6 (C=O), 175.1 (C=O) ppm. LC-MS: *m*/*z* = 470 [M + H]$^+$.

Boc-Aib-Phe-OEt (9): White solid. Yield 75% (43 mg). R_f = 0.62 (DCM/MeOH, 8:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH$_2$), 1.40 (s, 3 H, CH_3-*Aib*), 1.43 (s, 12 H, *t*Bu, CH_3-*Aib*), 3.03 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2Ph), 4.05 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH$_3$CH_2), 4.78 (m, 1 H, C*H*-Bn), 4.86 (br. s, 1 H, N*H*), 6.80 (br. s, 1 H, N*H*), 7.05−7.28 (m, 5 H, ArH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 25.3 (CH_3-*Aib*), 28.1 (*t*Bu), 28.6 (CH_3-*Aib*), 38.0 (CH_2-*Phe*), 53.2 (CH-*Phe*), 56.5 (C-*Aib*), 61.2 (CH_2), 80.0 (C-*t*Bu), 126.8 (Ar), 128.3 (Ar), 129.2 (Ar), 135.9 (Ar), 154.4 (Ar), 171.4 (C=O), 174.0 (C=O) ppm.

Boc-Aib-Val-OMe (10):[13] White solid. Yield 76% (36 mg). R_f = 0.60 (DCM/MeOH, 8:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 [d, $^3J_{H,H}$ = 7.1 Hz, 3 H, (CH_3)$_2$CH], 0.95 [d, $^3J_{H,H}$ = 7.1 Hz, 3 H, (CH_3)$_2$CH], 1.37 (s, 9 H, *t*Bu), 1.42 (s, 3 H, CH_3-*Aib*), 1.48 (s, 3 H, CH_3-*Aib*), 2.12 [m, 1 H, C*H*(CH$_3$)$_2$], 3.64 (OCH_3), 4.45 (dd, $^3J_{H,H}$ = 8, $^3J_{H,NH}$ = 5 Hz, 1 H, HNC*H*-*i*Pr), 4.90 (br. s, 1 H, N*H*), 6.95 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.4 (CH_3-*Val*), 18.8 (CH_3-*Val*), 26.0 (CH_3-*Aib*), 28.1 (*t*Bu), 29.5 (CH-*Val*), 31.2 (CH_3-*Aib*), 51.9 (OCH_3), 56.7 (C-*Aib*), 57.0 (NHCH-*Val*), 80.0 (C-*t*Bu), 172.4 (C=O), 174.3 (C=O) ppm.

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