# Solid phase synthesis of anhydrides and amides: polymer-assisted reaction in the synthesis of dipeptides

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Linear poly-4- and poly-2-vinylpyridines and copolymers of these with divinylbenzene have been used as an efficient solid phase for the synthesis of acid anhydrides and amides, by pyridinium catalyzed acyl transfer to carboxylic acids or amines, respectively, in equimolar amounts. (*S*,*S*)-CBZAla—Trp$CO_2$Me dipeptide was obtained in good yield in a multi-phase application.

Cross-linked copolymers of poly-4-vinylpyridine (P4VPy) obtained with styrene or 1,4-divinylbenzene and 4-vinylpyridine have been used as reagents.[1] These copolymers were found to be useful as hydrochloric acid acceptors[2] and as acylating reagents for specific acylation of coenzyme A.[3] However, linear homopolymers of 2- or 4-vinylpyridines and P2VPy copolymers have not received attention as polymeric supports.

Linear Ziegler–Natta homopolymerization of 2- or 4-vinylpyridine or copolymerization with 1,4-divinylbenzene (DVB) was performed by means of the Ziegler–Natta catalyst with the vanadium trichloride–aluminum triethyl system.[4] The linear polymers were fractionated in a continuous extraction with dichloromethane, followed by azeotropic elimination of water with toluene in a Dean–Stark trap.

Moreover, appreciable variations in the catalytic activity were observed when 2- or 4-vinylpyridines were added to the prior reaction between $VCl_3$–$AlEt_3$. We assume different coordination effects of the pyridine ring due to electronic but not sterical properties in the formation of the catalytic system.[4] In this way, we wished to analyse the behavior of the supported acylpyridinium on the 2- or 4-pyridine ring and the acyl transfer reaction to carboxylic acids or amines to prepare mixed acid anhydrides or amides, respectively, in a considerably simplified procedure. The same methodology can be extended to the synthesis of peptides.

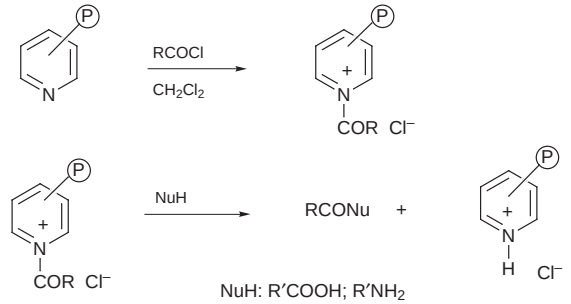
## Results and Discussion

The supported acylation was carried out in Schlenk tubes, with a molar excess of the appropriate PVPy in dichloromethane and an appropriate amount of the acylating reagent. The mixture was stirred for 30 min and then a stoichiometric amount of a nucleophile (carboxylic acid or amine) was added (absence of vigorous exothermicity); stirring was continued for 10 min. The reaction mixture was filtered off and the PVPy washed twice with dichloromethane. The extracts were washed with sodium bicarbonate (10%). After solvent elimination, the residual solid was recrystallized to obtain the pure anhydride (or amide) in good yield. The hydrochloric acid generated in the reaction was trapped by the corresponding excess of PVPy, which displaces the equilibrium toward the anhydride (or amide) formation. The saline supports PVPy·HCl were regenerated by stirring with a sodium hydroxide solution (10%), filtering and washing twice with water. Finally, the PVPy support was dried by azeotropic elimination of the water with toluene.

### Preparation of the mixed methoxybenzoic anhydrides in the solid phase

The benzoic-*n*-methoxybenzoic anhydrides were obtained pure in good yields by means of the PVPy supports, starting with benzoyl chloride and the appropriate methoxybenzoic acid, at room temperature (Table 1). A two-step mechanism[5] with an acylpyridinium ion as the intermediate has been established in the pyridine catalysed acyl transfer.[6] Thus, the anhydrization step proceeds by nucleophilic displacement of the supported *N*-acylium ion by the carboxylic acid (Scheme 1).

On the basis of the anhydride yield with these polymer supports, the reaction seems to be independent of the nitrogen atom position in the pyridine ring. Thus, the acylation and anhydrization steps show analogous steric hindrance for both pyridine rings using linear or cross-linked supports.




**Scheme 1** Mechanism of the acyl transfer; Ⓟ is the polyvinyl chain

**Table 1** Percent yields of the anhydride in the solid-phase anhydrization of methoxybenzoic acids with benzoyl chloride

| Anhydride | P4VPy | P2PVy | P4VPy-DVB[a] | P2VPy-DVB[a] |
|---|---|---|---|---|
| Benzoic-2-methoxybenzoic | 86 | 80 | 75 | 70 |
| Benzoic-3-methoxybenzoic | 80 | 77 | 70 | 68 |
| Benzoic-4-methoxybenzoic | 85 | 83 | 81 | 77 |

[a] Copolymers of vinylpyridine-DVB (1% mol).

The isotactic structure of P2VPy has been determined by X-ray diffraction methods.[7] The asymmetric unit consists of a threefold helix of three monomeric units in a hexagonal unit cell. Little differences were observed in the X-ray powder diffraction pattern of isotactic P4VPy and it was assumed that this would be consistent with an analogous threefold structure.

### Preparation of amides in solid phase

The same first step of acylation between the acyl chloride and the PVPy (linear or cross-linked) supports referred to in the anhydrization reaction has been undertaken in the amidation reaction, which requires treatment of the acylpyridinium salt with an amine at room temperature (Scheme 1). Table 2 shows the yield in pure amide for linear PVPy and cross-linked PVPy-DVB supports.

Pure amides were obtained in good to excellent yields and these seem to be independent of the relative positions of the nitrogen atom and the polyvinyl chain on the pyridine ring for both linear and cross-linked supports, and thus the acylation and amidation steps for both types of supports show a similar steric hindrance.

In addition, the formation of the amide from *o,m,p*-substituted aromatic amines having the same substituent (nitro, methoxy) seems to be independent of the p$K_a$ value as well as the position and electronic character of the substituent,[8,9] (Table 2). Synthetic microporous cross-linked PVPy-DVB supports give comparatively lower yields of the benzoylmethoxyanilide than the linear supports.

In connection with the amidation reaction, a multi-phase technique in organic synthesis was applied to the preparation of the peptide NHCO bond for *N*-protected (*S*)-alanine (Ala) and (*S*)-tryptophane methyl ester ($TrpCO_2Me$) on linear P4VPy as the support. In a first experiment the reaction was carried out on P4VPy (6 mequiv.) in dichloromethane with the protected BOCAla and $TrpCO_2Me$ in two consecutive reactions: (*i*) treatment of BOCAla with $SOCl_2$ for 5 min and (*ii*) addition of $TrpCO_2Me$ followed by stirring for 10 min. The P4VPy support was used as the acyl and hydrochloric acid acceptor (formation of BOCAla-acyl chloride in the presence of P4VPy fails in separate steps). Thus, BOCAla—$TrpCO_2Me$ dipeptide was obtained as an oil in 12% yield while important amounts of BOC-deprotected alanine and free $TrpCO_2Me$ were recovered.

In a similar multi-phase reaction, but with a higher excess of P4VPy (16 mequiv.) and using CBZ instead of BOC as the protecting group, the (*S,S*)-CBZAla—$TrpCO_2Me$ dipeptide was obtained practically pure by filtration and after column chromatography was isolated as a white solid $\{[\alpha]_D = -4.9°$ (MeOH at 32 °C)$\}$ in 75% yield.

## Experimental

Melting points were determined using a Reichert hotstage microscope and are uncorrected. IR spectra were obtained as neat films between NaCl plates or KBr pellets or a Nujol suspension. NMR spectra were recorded at 200 MHz using a Bruker WM-200-SY spectrometer, chemical shifts are given in δ, using TMS as internal reference. Mass spectra analyses were recorded by electron impact at 70 eV. Yields are given of the isolated products. Elemental analyses were performed with a LECO CHN-900.

### Preparation and analysis of the PVPy supports

**General procedure applied to P4VPy.** Into a flamed-sealed Schlenk tube under argon atmosphere were placed a suspension of $VCl_3$ (1.92 g, 14.8 mmol) in dry toluene (180 ml) and a 19 M solution of $AlEt_3$ in toluene (16.2 ml, 29.6 mmol). The mixture was stirred at room temperature for 30 min and then heated to 90 °C in a thermostated bath; freshly distilled 4-vinylpyridine (30 ml, 278 mmol) was then added and the mixture was stirred at 90 °C for 6 h. The mixture was cooled to room temperature, stirred with ethanol (30 ml) for 2 h, then poured onto water (500 ml) and stirred until the violet color of the polymer disappeared. The polymer was filtered and placed in a Dean–Stark apparatus to remove water by azeotropic distillation with toluene for 3 h. Afterwards the polymer was treated in continuous extraction (Soxhlet) with dichloromethane, dried under reduced presure and powdered to give the P4VPy (28 g, 96%), as a white–grey powder.

**Preparation of P2VPy.** Following the general procedure, freshly distilled 2VPy (10.16 ml, 94 mmol) in the same molar ratio of $VCl_3$–$AlEt_3$ gives P2VPy (5.3 g, 54%), as a grey–green powder.

**PVPy analyses.** The analyses of the crystallinity (X-ray), average molecular weight (viscometry) and melting range (DSC) of the linear polymers have been carried out: P2VPy, amorphous material, $C < 12\%$, $[\bar{M}_n] = 3.7–7.1 \times 10^4$ g melting range of 225–260 °C; P4VPy, crystalline material, *C*, 34–50%, $[\bar{M}_n] = 4.3–8.1 \times 10^4$ g, melting range of 255–290 °C.

**Preparation of P4VPy-DVB.** Following the general procedure, freshly distilled 4VPy (10.16 ml, 94 mmol) and divinylbenzene (1–10% mol), in the same molar ratio of $VCl_3$–$AlEt_3$, gives DVB-P2VPy copolymers, which after extraction with ethanol were separated as powdered grey solids in variable yields depending on the DVB amount:

| DVB | g, % mol | Yield/% |
|---|---|---|
| 0.123 | 1 | 61 |
| 0.246 | 2 | 75 |
| 0.615 | 5 | 42 |
| 1.23 | 10 | 31 |

**Table 2** Percent yields of the anilide in the solid-phase amidation of aromatic amines with benzoyl chloride

| Amide | p$K_a$ | P4VPy | P2VPy | P4VPy-DVB[a] | P2VPy-DVB[a] |
|---|---|---|---|---|---|
| Aniline | 4.63 | 80 | 74 | — | — |
| Benzylamine | 9.33 | 97 | 90 | — | — |
| 2-Nitroaniline | −0.26 | 81 | 79 | — | — |
| 3-Nitroaniline | 2.47 | 77 | 80 | — | — |
| 4-Nitroaniline | 1.00 | 80 | 80 | — | — |
| 2-Methoxyaniline | 4.52 | 95 | 90 | 67 | 60 |
| 3-Methoxyaniline | 4.23 | 94 | 87 | 59 | 52 |
| 4-Methoxyaniline | 5.34 | 95 | 93 | 60 | 52 |
| 3-Phenylaniline[b] | 4.25 | 90 | 93 | — | — |

[a] Copolymers of vinylpyridine-DVB (1% mol). [b] With ethyl chlorooxalate.

**Preparation of P2VPy-DVB.** Following the general procedure, freshly distilled 2VPy (10.16 ml) and divinylbenzene (1–2% mol), in the same molar ratio of $VCl_3$–$AlEt_3$, gives DVB-P2VPy copolymers, which after extraction with ethanol were separated as powdered slightly brown solids.

| DVB | (g, % mol | Yield % |
|---|---|---|
| 0.123 | 1 | 25 |
| 0.246 | 2 | 10 |

**PVPy-DVB analyses.** The copolymerizations of the vinylpyridine (2- or 4-) and the appropriate amount of DVB (1–10%) were carried out under the same catalyst system and after separation were first fractionated succesively with ethanol and then dried by azeotropic elimination of water with toluene. The PVPy-DVB copolymers were isolated as amorphous powders, which show thermal stability up 300 °C (decompose) and, by electronic microscopy, exhibit a microporous surface.

### Preparation of mixed anhydrides with PVPy supports

**General procedure applied to benzoic-2-methoxybenzoic anhydride.** To a suspension of PVPy (1.5 g, 14.2 mequiv.) in dry dichloromethane (20 ml) was added freshly distilled benzoyl chloride (0.49 g, 3.5 mmol) under argon atmosphere, at room temperature. The mixture was stirred for 30 min, 2-methoxybenzoic acid (0.54 g, 3.5 mmol) was then added and stirring continued for 10 min. The polymeric support was recovered by filtration, washed twice with 10 ml of dichloromethane and regenerated by treatment successively with NaOH (10%), washing twice with $H_2O$ and drying in a Dean–Stark trap with toluene for 3 h.

The dichloromethane extracts were washed with two portions of 10 ml of an aqueous solution of $NaHCO_3$ (10%). The organic layer was dried over magnesium sulfate and after filtration the solvent was removed under reduced pressure to give benzoic-2-methoxybenzoic anhydride (0.77 g, 86% with P4VPy support and 0.72 g, 80% with P2VPy support) as a white solid, mp 74–76 °C. (Found: C, 69.1; H, 4.8%. Calcd for $C_{15}H_{12}O_4$: C, 69.25; H, 4.65%); $\nu_{max}$ ($CHBr_3$) 1782 and 1725 (C=O), 1600 (C=C, conj.), 1040 (C—O—C), 776 (*o*-subst.), and 704 (monosubst.) $cm^{-1}$; NMR (200 MHz; $CDCl_3$) δ 4.1 (3H, s, $CH_3$), 7.0–8.3 (9H, m, ArH).

**Benzoic-3-methoxybenzoic anhydride.** Following the general procedure, benzoyl chloride (0.49 g, 3.5 mmol) and 3-methoxybenzoic acid (0.54 g, 3.5 mmol) give benzoic-3-methoxybenzoic anhydride (0.72 g, 80% with P4VPy support and 0.68 g, 77% with P2VPy support) as a yellow oil. (Found: C, 69.2; H, 4.9%. Calcd for $C_{15}H_{12}O_4$: C, 69.25; H, 4.65%); $\nu_{max}$ (film) 1780 and 1720 (C=O), 1600 (C=C, conj.), 1040 (C—O—C), 740 and 710 (*m*-subst.), 700 and 670 (monosubst.) $cm^{-1}$; 1H NMR (200 MHz; $CDCl_3$) δ 3.9 (3H, s, $CH_3$), 7.2–8.2 (9H, m, ArH).

**Benzoic-4-methoxybenzoic anhydride.** Following the general procedure, benzoyl chloride (0.49 g, 3.5 mmol) and 4-methoxybenzoic acid (0.54 g, 3.5 mmol) give benzoic-4-methoxybenzoic anhydride (0.76 g, 85% with P4VPy support, and 0.74 g, 83% with P2VPy support) as a white solid, mp 95–99 °C. (Found: C, 68.9; H, 4.9%. Calcd for $C_{15}H_{12}O_4$: C, 69.25; H, 4.65%); $\nu_{max}$ ($CHBr_3$) 1785 and 1722 (C=O), 1600 (C=C, conj.), 1040 (C—O—C), 841 (*p*-subst.), and 703 (monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) 4.0 (3H, s, $CH_3$), 6.9–8.4 (9H, m, ArH).

### Preparation of *N*-phenylbenzamide with PVPy as supports

**General procedure applied to *N*-phenylbenzamide.** To a suspension of PVPy (1.56 g, 14.8 mequiv.) in dry dichloromethane (20 ml) was added freshly distilled benzoyl chloride (0.52 g, 3.7 mmol) under argon atmosphere at room temperature. The mixture was stirred for 30 min, freshly distilled aniline (0.35 g, 3.7 mmol) was then added and stirring continued for 10 min. The mixture was filtered and washed twice with 10 ml of dichloromethane. The extracts were washed successively with two portions of 10 ml of an aqueous solution of $NaHCO_3$ (10%). The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure; the white residue was recrystallized from hexane : ethanol (4 : 1) to give *N*-phenylbenzamide (0.58 g, 80% with P4VPy support and 0.53 g, 74% with P2VPy support) as colorless crystals, mp 162–163 °C (lit.[10] 162 °C). $\nu_{max}$ ($CHCl_3$) 3340 (NH), 1654 (C=O), 1523 (NC=O), 1257 (C—N), 1597 (C=C, conj.), 748 and 688 (monosubst) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 7.1–8.2 (10H, m, ArH), 7.95 (1H, br s, NH); *m/z* 197 ($M^+$, 21), 105 (100), 77 (92).

***N*-Benzylbenzamide.** Benzoyl chloride (0.93 g, 6.7 mmol) and benzylamine (0.71 g, 6.7 mmol) give *N*-benzylbenzamide (1.37 g, 97% with P4VPy support and 1.27 g, 90% with P2VPy support) as a white solid, mp 104–105°C (lit.[11] 104–105 °C). $\nu_{max}$ ($CHCl_3$) 3441 (NH), 1655 (C=O), 1516 (NC=O), 1293 (C—N), 1594 (C=C, conj.), 747 and 700 (monosubst.), 1480 ($CH_2$), 1430 ($CH_2$—C=C) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 4.6 (2H, d, $CH_2$—NH, *J* 7.0 Hz), 6.6 (1H, br s, NH), 7.2–8.2 (10H, m, ArH); *m/z* 211 ($M^+$, 40), 105 (100), 77 (98).

***N*-(2-Nitrophenyl)benzamide.** Benzoyl chloride (0.3 g, 2.2 mmol) and 2-nitroaniline (0.3 g, 2.2 mmol) give *N*-(2-nitrophenyl)benzamide (0.43 g, 81% with P4VPy support and 0.42 g, 79% with P2VPy support) as a yellow solid, mp 96–97 °C (lit.[12] 98 °C). $\nu_{max}$ ($CHCl_3$) 3365 (NH), 1680 (C=O), 1580 (NC=O), 1500 and 1340 ($NO_2$), 1220 (C—N), 775 and 665 (*o*-subst. and monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 7.1–9.0 (9H, m, ArH and 1H, NH); *m/z* 242 ($M^+$, 13), 196 (27), 105 (100), 77 (78).

***N*-(3-Nitrophenyl)benzamide.** Benzoyl chloride (0.25 g, 1.7 mmol) and 3-nitroaniline (0.25 g, 1.7 mmol) give *N*-(3-nitrophenyl)benzamide (0.31 g, 77% with P4VPy support and 0.28 g, 70% with P2VPy support) as a white solid, mp 155–157 °C (lit.[13] 157 °C). $\nu_{max}$ ($CHCl_3$) 3359 (NH), 1660 (C=O), 1595 (NC=O), 1526 and 1352 ($NO_2$), 1260 (C—N), 798, 735 and 690 (*m*-subst. and monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 7.5–8.5 (9H, m, ArH), 8.2 (1H, br s, NH); *m/z* 242 ($M^+$, 8), 105 (100), 77 (84).

**N-(4-Nitrophenyl)benzamide.** Benzoyl chloride (0.25 g, 1.7 mmol) and 4-nitroaniline (0.25 g, 1.7 mmol) give *N*-(4-nitrophenyl)benzamide (0.32 g, 80% with P4VPy support and 0.32 g, 80% with P2VPy support) as a yellow solid, mp 197–199 °C (lit.[14] 199 °C). $\nu_{max}$ ($CHCl_3$) 3333 (NH), 1651 (C=O), 1611 (NC=O), 1500 and 1301 ($NO_2$), 1253 (C—N), 847 (*p*-subst.), 748 and 690 (monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 7.3–8.3 (9H, m, ArH), 8.1 (1H, br s, NH); *m/z* 242 ($M^+$, 5), 105 (100), 77 (85).

***N*-(2-Methoxyphenyl)benzamide.** Benzoyl chloride (0.34 g, 2.4 mmol) and 2-methoxyaniline (0.30 g, 2.4 mmol) give *N*-(2-

methoxyphenyl)benzamide (0.52 g, 95% with P4VPy support and 0.49 g, 90% with P2VPy support) as colorless crystals, mp 59–60 °C (lit.[15] 60 °C). $\nu_{max}$ (film) 3426 (NH), 2838 ($OCH_3$), 1671 (C=O), 1601 (C=C, conj.), 1530 (NC=O), 1254 (C—N), 750 and 709 (*o*-subst. and monosubst.), 1290 and 1026 (ArC—O—C), 1450 and 1431 ($CH_3$) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 3.9 (3H, s, $CH_3$), 6.8–8.7 (9H, m, ArH and 1H, NH); *m/z* 227 ($M^+$, 16), 196 (2), 105 (100), 77 (81).

***N*-(3-Methoxyphenyl)benzamide.** Benzoyl chloride (0.34 g, 2.4 mmol) and 3-methoxyaniline (0.30 g, 2.4 mmol) give *N*-(3-methoxyphenyl)benzamide (0.51 g, 94% with P4VPy support and 0.47 g, 87% with P2VPy support) as a white solid, mp 103–105 °C. (Found: C, 73.7; H, 5.5; N, 5.9%. $C_{14}H_{13}NO_2$ requires: C, 73.99; H, 5.77; N, 6.16%); $\nu_{max}$ ($CHBr_3$) 3423 (NH), 2833 ($OCH_3$), 1667 (C=O), 1602 (C=C, conj.), 1528 (NC=O), 1452 and 1421 ($CH_3$), 1210 (C—N), 1274 and 1039 (ArC—O—C), 775, 746 and 700 (*m*-subst. and monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) 3.8 (3H, s, $CH_3$), δ 6.6–8.0 (9H, m, ArH), 7.9 (1H, br s, NH); *m/z* 227 ( $M^+$, 20), 105 (100), 77 (52).

***N*-(4-Methoxyphenyl)benzamide.** Benzoyl chloride (0.49 g, 3.5 mmol) and 4-methoxyaniline (0.43 g, 3.5 mmol) give *N*-(4-methoxyphenyl)benzamide (0.75 g, 95% with P4VPy support and 0.73 g, 93% with P2VPy support) as a white solid, mp 155–156 °C (lit.[16] 153–154 °C). $\nu_{max}$ ($CHCl_3$) 3327 (NH), 2833 ($OCH_3$), 1662 (C=O), 1605 (C=C, conj.), 1513 (NC=O), 1443 and 1409 ($CH_3$), 1248 (C—N), 1298 and 1034 (ArC—O—C), 825 and 691 (*p*-subst. and monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 3.8 (3H, s, $CH_3$), 6.8–7.9 (9H, m, ArH and 1H, NH); *m/z* 227 ($M^+$, 22), 122 (12), 105 (100), 77 (99).

**Ethyl-*N*-(3-biphenyl)amidoxalate.** Ethyl chlorooxalate (0.17 g, 1.23 mmol) and 3-phenylaniline (0.21 g, 1.23 mmol) give ethyl-*N*-(3-biphenyl)amidoxalate (0.29 g, 90% with P4VPy support and 0.30 g, 93% with P2VPy support) as a brown oil. (Found: C, 71.2; H, 5.4; N, 4.9%. $C_{16}H_{15}NO_3$ requires: C, 71.36; H, 5.61; N, 4.98%); $\nu_{max}$ ($CHCl_3$) 3480 (NH), 1710 (C=O, ester), 1690 (C=O, amide), 1600 (C=C, conj.), 1550 (NC=O), 1480 and 1375 ($CH_2$ and $CH_3$), 1265 (C—N), 1310 and 1020 (C—O), 760, 700 and 665 (*m*-subst. and monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 1.3 (3H, t, $CH_3$, *J* 8.3 Hz), 4.4 (2H, q, $CH_2$, *J* 8.3 Hz), 7.1–8.0 (9H, m, ArH), 9.0 (1H, br s, NH); *m/z* 269 ($M^+$, 100), 196 (96), 168 (48), 152 (66).

### Application of P4VPy as support to the synthesis of (*S*,*S*)-CBZAla—TrpCO$_2$Me

To a suspension of P4VPy (1.68 g, 16 mequiv.) in dry dichloromethane (20 ml) were successively added (*S*)-CBZ-alanine (0.24 g, 1.05 mmol) and thionyl chloride (0.1 ml, 1.26 mmol) under argon at room temperature. The mixture was stirred for 20 min. Then, (*S*)-tryptophane methyl ester (0.23 g, 1.05 mmol) was added and 15 min later the reaction mixture was filtered and washed twice with 10 ml of dichloromethane. The solvent was then evaporated to give a white solid, which was purified by chromatography on silica gel, using *n*-hexane : ethyl acetate (1 : 2) as the eluent to give the dipeptide as colorless prismatic crystals (0.33 g, 75%), mp 119 °C, $[\alpha]_D = -4.9°$ (MeOH, 32 °C); $\nu_{max}$ (KBr) 3320 (NH), 1750 (C=O, ester), 1680 (C=O, carbamate), 1640 (C=O, amide), 1540 (N-C=O), 800 and 760 (*o*-disubst. indole), 750 and 720 (monosubst.) $cm^{-1}$; $^1H$ NMR (200 MHz; $CDCl_3$) δ 1.3 (3H, d, $CH_3$—CH, *J* 7.0 Hz), 3.3 (2H, d, indole-$CH_2$, *J* 5.3 Hz), 3.7 (3H, s, $CH_3O$), 4.2 (1H, m, $CH_3CHNH$), 4.9 (1H, dt, $CH_2CHNH$, $J_{H-NH}$ 8.0 Hz, $J_{H-CH_2}$ 5.3 Hz), 5.0 (2H, s, $CH_2Ph$), 5.2 (1H, d, $NHCHCH_3$, *J* 7.3 Hz), 6.53 (1H, d, $NHCHCH_2$, *J* 8.0 Hz), 6.9 (1H, s, H-2), 7.1 (2H, m, H-6 and H-7), 7.3 (1H, d, H-8, *J* 7.4 Hz), 7.4 (5H, s, Ph), 7.5 (1H, d, H-5, *J* 7.7 Hz), 8.0 (1H, br s, indole-NH); *m/z* 423 ($M^+$, 7), 315 (11), 201 (64), 185 (6), 170 (14), 130 (100), 115 (6), 108 (14), 91 (25), 77 (17).

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