Electronic Supplementary Information

Coupling reaction between electron-rich pyrimidinones and \(\alpha\)-amino acids promoted by phosphonium salts

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<td>18c</td>
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<tr>
<td>12b</td>
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Instruments

High performance liquid chromatography (HPLC) was performed on a Summit Dionex instruments composed of P680 binary pump, UVD 170U 4-Channel UV-Vis Detector, ASI-100 Autosampler and the Chromaleon 6.60 software from Dionex, on a C18 Kromasil reverse-phase column (4.6 x 40 mm; 3.5 µm particle size). ESI-MS analyses were performed with an Esquire 6000 ESI ion Trap LC/MS (Bruker Daltonics) instrument equipped with an electrospray ion source. The instrument was operated in the positive ESI(+) ion mode.

Analysis of optical purity of pyrimidin-4-yl amino esters 12

The optical purity of compounds 12 was verified by coupling with both racemic phenylalanine and L-phenylalanine in order to measure the degree of racemisation by HPLC. Thus, samples of Nα-Boc amino esters 12 were deprotected using lithium hydroxide to give amino acids 19 in near quantitative yield. These compounds were first coupled to resin bound racemic phenylalanine 20a using standard protocols for solid-phase peptide synthesis following Fmoc/tert-butyl strategy. After cleavage from the resin, the HPLC analyses of the resulting dipeptides 20a showed the formation of two diastereoisomers. Dipeptides 20b were then synthesized analogously by coupling Nα-Boc amino acids 12 to L-phenylalanine resin bound 20b. When no reasonable racemisation occurred during the synthesis of 12, HPLC analyses of 20b showed the formation of one single diastereoisomer (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Solid-phase synthesis of dipeptides 20. Reagents and conditions: (a) LiOH, THF/MeOH/H₂O (1:2:2), room temp., 3-4 h. (b) (i) HBTU, DIEA, DMF, room temp., 3 h; (ii) TFA/H₂O/TIS (95:2.5:2.5), room temp., 2 h.

1 Optical purity of compounds 10 and 12e was also verified following Scheme 2.
Synthesis of Dipeptides 20 General procedure. Dipeptides 20 were prepared manually by solid-phase method using Fmoc-Rink-MBHA resin (0.64 mmol/g) as solid support following standard Fmoc-strategy. Coupling of amino acids were mediated by HBTU (3 equiv) and DIEA (3 equiv) in DMF at room temperature for 3 h. Monitoring was carried out by ninhydrin test. Washings were performed with DMF (6 x 1 min). Fmoc group was removed by treating the resin with 30% piperidine in DMF (v/v) and washed with DMF (6 x 1 min). The Fmoc-Rink-MBHA resin (10 mg) was placed into a plastic syringe fitted with a polypropylene frit to remove the Fmoc group and subsequently couple Fmoc-Phe-OH. After Fmoc group removal resin was treated with pyrimidinyl amino acid 19 under coupling conditions. The resulting dipeptides were deprotected and cleaved from resin by treatment with TFA/H2O/TIS (95:2.5:2.5) for 2 h. Then the solvents were evaporated to dryness and the crude dipeptides 20 were dissolved in H2O, lyophilized and tested for purity on HPLC. Electrospray ionisation mass spectrometry was used to confirm peptide identity.

HPLC conditions
Solvent A: H2O/0.1% TFA
Solvent B: CH3CN/0.1% TFA
Linear gradient of (2-100%) B at flow rate of 1.0 mL/min over 17 min.

HPLC of dipeptide 20a (12b)

Reaction performed with conditions D at 50°C (entry 6, Table 3)

HPLC of dipeptide 20b (12b)
HPLC of dipeptide 20a (12c)

Reaction performed with conditions B at 50ºC (entry 7, Table 3)

HPLC of dipeptide 20b (12c)

Reaction performed with conditions B at 50ºC (entry 7, Table 3)
HPLC of dipeptide 20b (12c)

Reaction performed with conditions D at 40°C (entry 10, Table 3)
$^1$H-NMR of compound 7a
$^{13}$C-NMR and DEPT experiment of compound 7a
$^1$H-NMR of compound 7b
$^{13}$C-NMR and DEPT experiment of compound 7b
$^1$H-NMR of compound 7c
$^{13}$C-NMR and DEPT experiment of compound 7c
$^1$H-NMR of compound 7e
$^{13}$C-NMR and DEPT experiment of compound 7e
$^1\text{H-NMR}$ of compound 8
\(^{13}\text{C}-\text{NMR and DEPT experiment of compound 8}\)
$^1$H-NMR of compound 10
$^{13}$C-NMR and DEPT experiment of compound 10
\(^1\text{H-NMR of compound 11}\)

![NMR Spectrum](image)

(200 MHz, CDCl₃)
$^{13}$C-NMR and DEPT experiment of compound 11
$^1$H-NMR of compound 16aa
$^{13}$C-NMR and DEPT experiment of compound 16aa
$^1$H-NMR of compound 16ab
$^{13}$C-NMR and DEPT experiment of compound 16ab
$^1$H-NMR of compound 16ac

![NMR Spectrum of Compound 16ac]

- Chemical shifts and peak assignments are shown.
- The spectrum is recorded at 400 MHz in CDCl$_3$.

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$^{13}$C-NMR and DEPT experiment of compound 16ac
$^1$H-NMR of compound 16ae

![NMR spectrum of compound 16ae]
$^{13}$C-NMR and DEPT experiment of compound 16ae
\(^1\text{H-NMR of compound 16ba}\)
$^{13}$C-NMR and DEPT experiment of compound 16ba
$^1$H-NMR of compound 16bb
$^{13}$C-NMR and DEPT experiment of compound 16bb
$^1$H-NMR of compound 16bc
$^{13}$C-NMR of compound 16bc
$^1$H-NMR of compound 16bd
$^{13}$C-NMR and DEPT experiment of compound 16bd
$^1$H-NMR of compound 16be
\(^{13}\)C-NMR and DEPT experiment of compound 16be
$^1$H-NMR of compound 17b
\(^{13}\)C-NMR and DEPT experiment of compound 17b
$^{1}H$-NMR of compound 12a
$^{13}$C-NMR of compound 12a
\(^1\text{H-NMR of compound 12b}\)

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\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{12b} \\
(400 \text{ MHz, CDCl}_3)
\end{array}
\]
$^{13}$C-NMR and DEPT experiment of compound 12b
$^1$H-NMR of compound 12c
$^{13}$C-NMR and DEPT experiment of compound 12c
$^1$H-NMR of compound 12d
$^{13}$C-NMR of compound 12d
HSQC-ed experiment of compound 12d
$^1$H-NMR of compound 12e
$^{13}$C-NMR and DEPT experiment of compound $12e$
$^1$H-NMR of compound 18a
$^{13}$C-NMR and DEPT experiment of compound 18a
$^1$H-NMR of compound 18b
$^{13}$C-NMR and DEPT experiment of compound 18b
$^1$H-NMR of compound 18c
$^{13}$C-NMR and DEPT experiment of compound 18c

![S58](image)
HSQC-ed experiment of compound 18c
NOESY experiment of compound 12b