Native Chemical Ligation by Microflow Chemistry

Microfluidic system:

feed solution 1

pPeptide SEA^{on} (7 mM)

TCEP (100 mM), pH 1

CyslleLeuLysGluProValHisGlyVal-SEA^{on}
CyslleLeuLysGluGlyValHisGlyVal-SEA^{on}
CyslleLeuAsnGlyProValHisGlyVal-SEA^{on}
CyslleLeuAspGlyProValHisGlyVal-SEA^{on}
CyslleLeuAsnGlyProValHisGlyLeu-SEA^{on}
CyslleLeuAspGlyProValHisGlyLeu-SEA^{on}
CyslleLeuLysGluGlyValHisGlyThr-SEA^{on}
CyslleLeuLysGluGlyValHisGlyIle-SEA^{on}
CyslleLeuLysGluGlyValHisGlyPro-SEA^{on}

feed solution 2

decane

$t^1 = 60 \text{ min}$

$T^1 = 90^\circ\text{C}$ or 65°C

cyclic peptides

c-(CyslleLeuLysGluProValHisGlyVal) (46%)
c-(CyslleLeuLysGluGlyValHisGlyVal) (46%)
c-(CyslleLeuAsnGlyProValHisGlyVal) (66%)
c-(CyslleLeuAspGlyProValHisGlyVal) (37%)
c-(CyslleLeuAsnGlyProValHisGlyLeu) (80%)
c-(CyslleLeuAspGlyProValHisGlyLeu) (64%)
c-(CyslleLeuLysGluGlyValHisGlyThr) (49%)
c-(CyslleLeuLysGluGlyValHisGlyIle) (51%)
c-(CyslleLeuLysGluGlyValHisGlyPro) (38%)

feed solution 3

MPAA (0.4 M)

Na₂HPO₄ (0.2 M)

pH = 7.8

pH = 7.3
 $t^2 = 4 \text{ min}$
 $T^2 = 37^\circ\text{C}$

BPR

2.5 bar

workup 2 (if necessary)

workup 1 (all)

acidification with 10% aq AcOH
then extraction with Et₂O

HPLC

Significance: The authors reported a fast and highly efficient intramolecular cyclization of peptides with native chemical ligation under homogeneous microfluidic conditions, in which the formation of highly active S-[2-[(2-sulfanylethyl)amino]-ethyl] peptidyl thioesters is a key step.

Comment: This scale-independent microfluidic native chemical ligation proceeds rapidly, even for difficult junctions, and realizes an expedient preparation of bioactive macrocyclic peptides.

SYNFACTS Contributors: Hisashi Yamamoto, Takahiro Sawano

Synfacts 2019, 15(02), 0203 Published online: 18.01.2019

DOI: 10.1055/s-0037-1611960; Reg-No.: H17518SF

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Category

Peptide Chemistry

Key words

native chemical
ligation

cyclic peptides

microflow reaction

flow synthesis

thioesters

Synfact
of the
Month