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Peptide Ligation by Chemoselective Aminonitrile Coupling in Water
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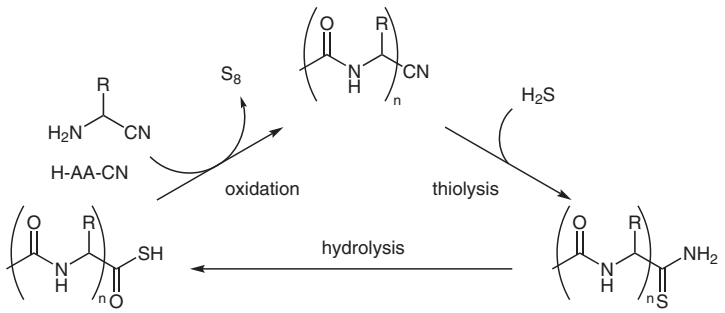
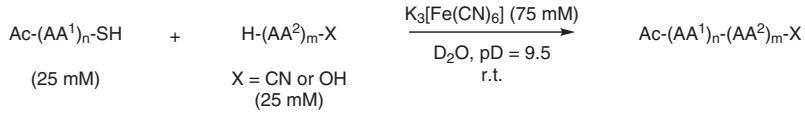
Sulfide-Mediated Peptide Ligation in Water

Ligation cycle:

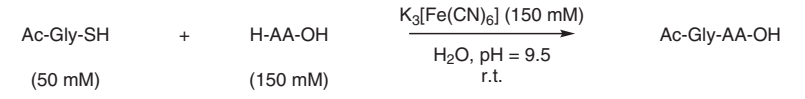


Synthesis of oligomeric *N*-acetyl peptides and peptide nitriles by oxidative fragment ligation:



$(AA^1)_n$	H-$(AA^2)_m$-X	yield (%)	$(AA^1)_n$	H-$(AA^2)_m$-X	yield (%)
Gly	H-Gly-CN	71	Gly_3	H-Leu_3-OH	70
Gly_3	H-Ala_3-OH	65	Gly_3	Phe-Gly_2-OH	74
Gly_3	Arg-Gly-Asp-OH	76	Gly_3	Met-Ala-Ser-OH	75
Gly_3	H-Gly_3-OH	90	Gly_5	H-Ala_3-OH	74
Gly_3	H-Gly_3-CN	>95	Gly_5	Gly_2-His-OH	80

Synthesis of *N*-acetyl dipeptides:



AA	yield (%)	AA	yield (%)	AA	yield (%)
Gly	94	Asp	89	Ile	84
Ala	83	Gln	90	Leu	86
Arg	88	Glu	92	Met	95
Asn	81	His	95	Pro	89
Phe	90	Ser	85	Thr	81

Significance: This work provides a method for achieving α-peptide ligation in water that tolerates all 20 proteinogenic amino acids. This is extremely important, especially in biochemistry and the life sciences.

Comment: The authors have developed a method for chemoselective α-aminonitrile ligation in water that uses prebiotically plausible molecules such as hydrogen sulfide, thioacetate, and ferricyanide. The α-peptides are obtained in good to high yields. The model suggests that short *N*-acyl peptides might have served as plausible substrates during the early evolution of life.

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Category
Peptide Chemistry

Key words
peptide ligation
aminonitriles
hydrogen sulfide
thioacetates
ferricyanides
aqueous media