O-to-*O* Acyl Transfer for Epimerization-free Peptide C-terminal Salicylaldehyde Ester Synthesis

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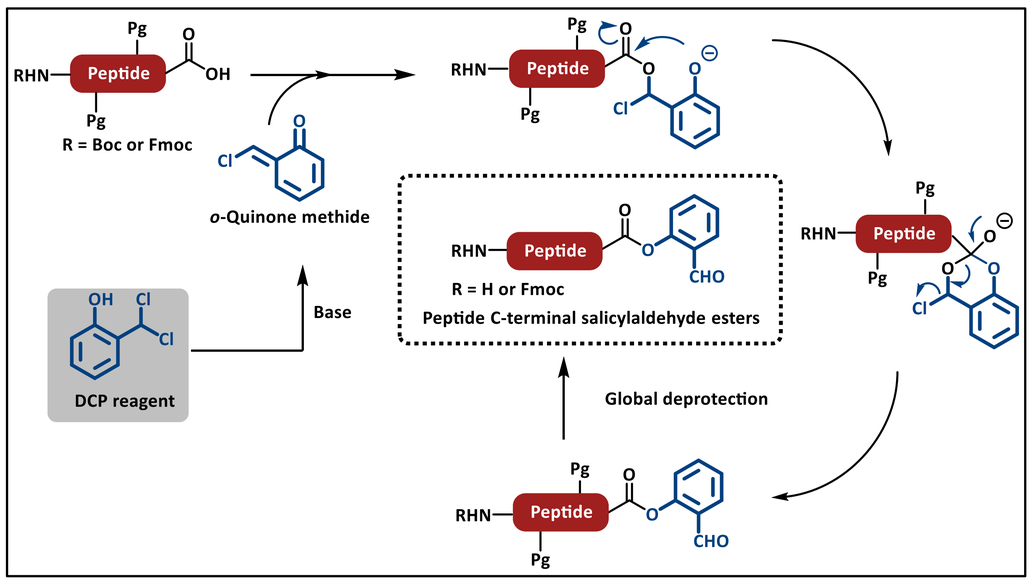
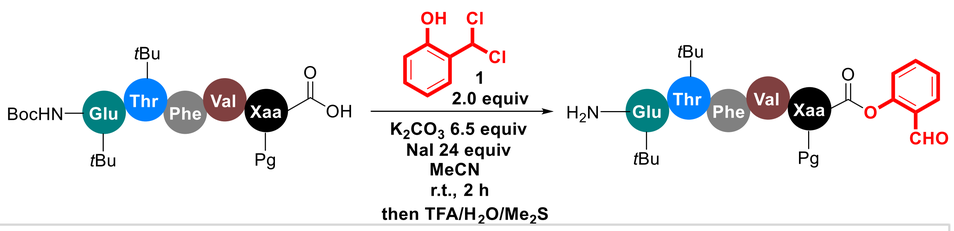
Abstract

Peptide salicylaldehyde esters are the requisite coupling partner in Ser/Thr ligation reactions towards chemical protein synthesis. In general, it would be cost-effective and efficient to use side chain protected peptide acids, after Fmoc-solid phase peptide synthesis, for direct C-terminal derivatization, however this has yet to be achieved, due to an intrinsic epimerization pathway. Here, we report the development of 2-(dichloromethyl)phenol (DCP) as a reagent which can directly form peptide salicylaldehyde esters in an epimerization-free manner. The peptide salicylaldehyde ester reaction products have been applied in the convergent total chemical synthesis of linker histone H1.2 using sequential Ser/Thr ligation reactions.



Results and Discussion



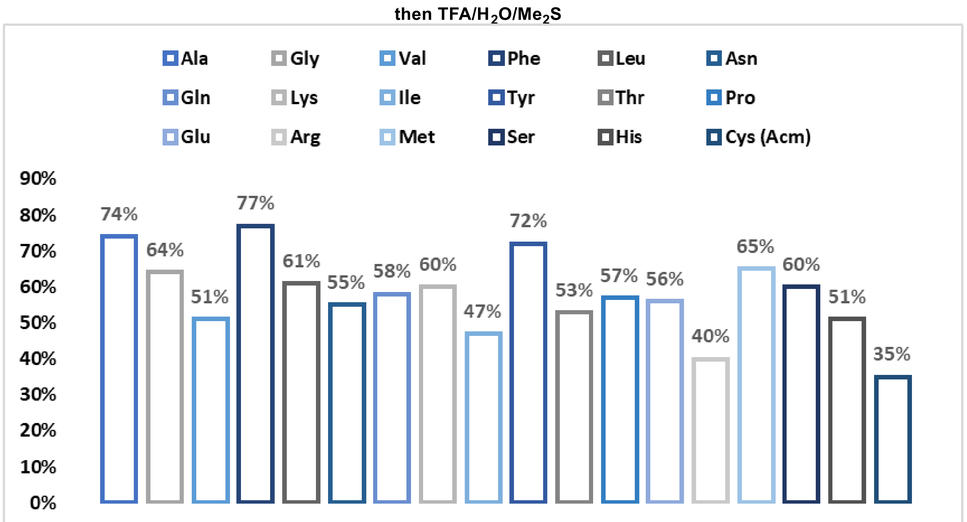
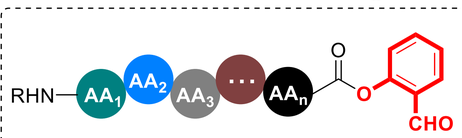


Figure 1. *Peptide SAL ester formation of different C-terminal residues using DCP reagent.*



Condition A: *DCP 2.0 equiv, K_2CO_3 6.5 equiv, NaI 24.0 equiv, MeCN*

Condition B: *DCP 3.0 equiv, K_2CO_3 10.0 equiv, NaI 24.0 equiv, MeCN/DCM 1/4 v/v*

Condition C: *DCP 5.0 equiv, K_2CO_3 24.0 equiv, NaI 30.0 equiv, MeCN/DCM 1/4 v/v*

Sequence	Number of AA	Method applied	Isolated yield
NH_2-TNNDTGEYF-COSAL	9	B	68%
NH_2-SAKGVRYQNA-COSAL	10	C	55%
NH_2-TARKLGDQITHAPDEVNRSG-COSAL	20	C	31%
NH_2-TMSAKEKGKFEDMAKADKARYEREM-COSAL	25	C	30%
NH_2-SELLSGMGVSALEKEEPDSENIPQELL-COSAL	27	C	32%
NH_2-PRNGTVHLYLTKPLYTSAPSLQHLC$_{StBu}$RL-COSAL	27	C	20%
NH_2-TYIPPKGETKKKFKDPNAPKRPPSAFFLF-COSAL	29	C	37%
NH_2-AFYRDPGVHAGLIYSAGVRKVILGQTNKGA-COSAL	30	C	28%
NH_2-PGLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEG-COSAL	37	C	27%

Figure 2. *Substrate scope of the peptide SAL ester formation using DCP reagent.*

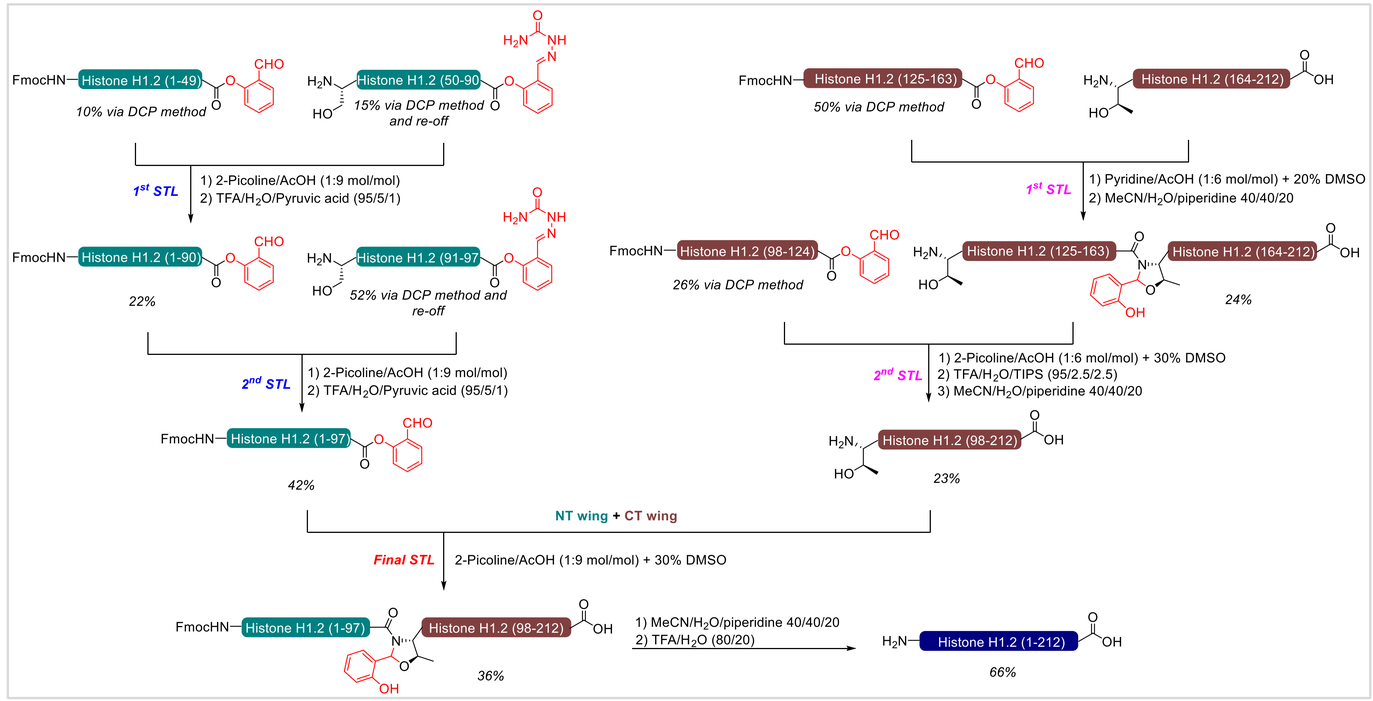


Figure 3. *Convergent synthesis of Histone H1.2 via serine/threonine ligations.*

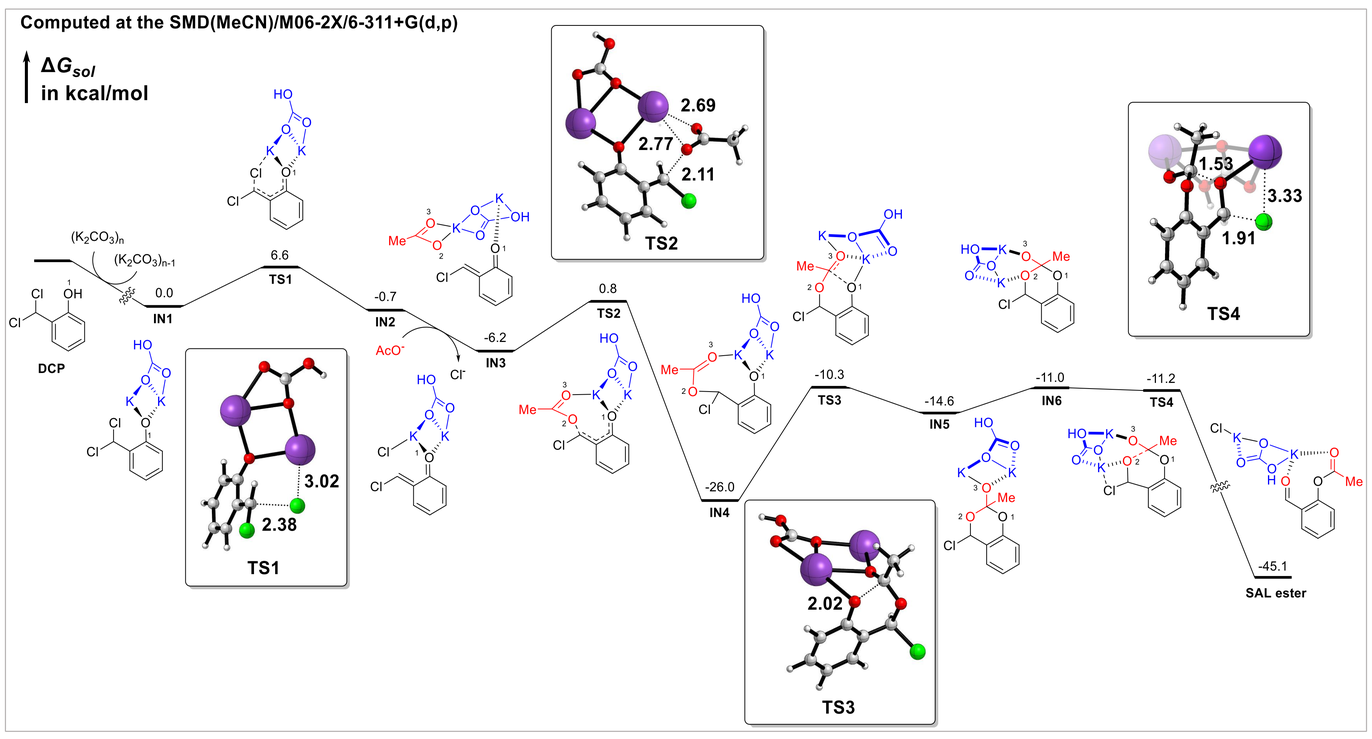


Figure 4. *Computational study of the mechanism*

Conclusion

The epimerization-free synthesis of peptide C-terminal salicylaldehyde (SAL) esters is achieved directly from solid phase synthesized side chain protected peptides using 2-(dichloromethyl)phenyl (DCP) reagent via a nontypical *O*-to-*O* acyl transfer. The scope of this method was demonstrated with syntheses of peptide SAL esters of various lengths ranging from 5 to 49 amino acids. The resulting peptide SAL esters were successfully applied for the convergent total chemical synthesis of 212-residue linker histone H1.2 protein using serine/threonine ligations.

References

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