chain" or other group as part of its structure that may also have to be protected. However, those skilled in the art will appreciate how such side chains or other group may be constructed, protected, and subsequently de-protected during the synthesis process.)

While this SPPS process is used commercially and is still the standard in peptide synthesis, it has a drawback in that it is expensive and time consuming. Each amino acid that is added must be de-protected and coupled, which is difficult and usually results in large quantities of solvents being used. Making matters worse is that many of these solvents are not environmentally friendly.

Accordingly, it would be an improvement to find a new way to use SPPS, that would address one or more of these deficiencies, especially in the commercial manufacturing of peptides. It would be a further advancement if such a system could be more environmentally friendly and reduce manufacturing costs. In fact, the present embodiments will specifically reduce the quantity of waste, and the quantity of solvent and reagents that are used. Such a method and system is disclosed herein.

SUMMARY

In one aspect of the present disclosure, there is provided a process for coupling amino acid "X" to a protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a protected N-group attached to a peptide synthesis resin;

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor;

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor;

removing the second quantity of de-protecting reagent from the second reactor;

washing the peptide synthesis resin in both the first and second reactors with a solvent;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor;

removing the second quantity of amino acid “X” activated ester from the second reactor; and

washing the peptide synthesis resin in both the first and second reactors with a solvent.

In another aspect of the present disclosure, there is provided a process for coupling amino acid “X” to a protected N-group that is attached to a peptide synthesis resin found in a first reactor and a second reactor arranged in series, comprising:

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor;

removing the second quantity of de-protecting reagent from the second reactor;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor;

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor; and

removing the second quantity of amino acid “X” activated ester from the second reactor.

In a further aspect of the present disclosure, there is provided a process for coupling amino acid “X” to a de-protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a de-protected N-group attached to a peptide synthesis resin;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor;

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor; and

removing the second quantity of amino acid “X” activated ester from the second reactor.

In another aspect of the present disclosure, there is provided a process for de-protecting a protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a protected N-group attached to a peptide synthesis resin;

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor;

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor; and

removing the second quantity of de-protecting reagent from the second reactor.

A process and system for coupling an amino acid “X” activated ester to a protected N-group (such as an NH_2 terminus) of an amino acid that is attached to a SPPS resin. Generally, the system will comprise a collection of reactors that are arranged in

series. In some examples, two or more reactors are arranged in series. In a preferred example, 3 or more reactors are arranged in series.

Each reactor contains a quantity of a protected N-group affixed to a peptide synthesis resin. This protected N-group may be an NH_2 group of an amino acid or may be an NH_2 group found on or covalently attached to the resin itself such as, but not limited to Sieber amide or Rink Amide resins. Other types of resins, such as Wang resins or CTC (chlorotrityl chloride) resins may also be used.

The first step in the process involves adding a first quantity of de-protecting reagent to the first reactor and allowing this reagent to contact the protected N-group. Then, this first quantity of de-protecting reagent is transferred from the first reactor to the second reactor and a second quantity of de-protecting reagent to the first reactor. The first quantity of de-protecting reagent is removed from the second reactor and the second quantity of de-protecting reagent is transferred from the first reactor to the second reactor. This second quantity of de-protecting reagent is then removed from the second reactor.

CLAIMS

1. A process for coupling amino acid “X” to a protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a protected N-group attached to a peptide synthesis resin;

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor;

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor;

removing the second quantity of de-protecting reagent from the second reactor;

washing the peptide synthesis resin in both the first and second reactors with a solvent;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor;

removing the second quantity of amino acid “X” activated ester from the second reactor; and

washing the peptide synthesis resin in both the first and second reactors with a solvent.

2. The process of claim 1, wherein the amino acid “X”, that is found in the first and second quantity of amino acid “X” activated ester, itself has a protected N-group.

3. The process of claim 1, further comprising:

adding the first quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin; and

adding the second quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor.

4. The process of claim 3, further comprising:

adding the first quantity of amino acid “X” activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the second reactor; and

adding the second quantity of amino acid “X” activated ester to the third reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the second reactor.

5. The process of claim 4, further comprising:

adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and

transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor; and

transferring the third quantity of de-protecting reagent from the second reactor to the third reactor; and

removing the third quantity of de-protecting reagent from the third reactor.

6. The process of claim 5, further comprising:

adding a third quantity amino acid “X” activated ester to the first reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor;

transferring the third quantity of amino acid “X” activated ester to the second reactor, wherein this transferring occurs after the second quantity of amino acid “X” activated ester is removed from the second reactor;

transferring the third quantity of amino acid “X” activated ester from the second reactor to the third reactor; and

removing the third quantity of amino acid “X” activated ester from the third reactor.

7. The process of claim 6, further comprising:

removing the first quantity of amino acid “X” activated ester from the third reactor; and

adding the first quantity of amino acid “X” activated ester back to first reactor.

8. The process of claim 7, further comprising:

removing the first quantity of de-protecting reagent from the third reactor; and adding the first quantity of de-protecting reagent back to the first reactor.

9. The process of claim 1, wherein the washing the first and second reactors with a solvent occurs by adding solvent to the reactors.

10. The process of claim 2, wherein after the second quantity of amino acid “X” activated ester has been removed from the first reactor, the method further comprising:

adding a first additional quantity of de-protecting reagent to the first reactor;

transferring the first additional quantity of de-protecting reagent from the first reactor to the second reactor;

adding a second additional quantity of de-protecting reagent to the first reactor;

removing the first additional quantity of de-protecting reagent from the second reactor;

transferring the second additional quantity of de-protecting reagent from the first reactor to the second reactor;

removing the second additional quantity of de-protecting reagent from the second reactor.

11. The process of claim 12 wherein after the second additional quantity of de-protecting reagent is removed from the first reactor, further comprising:

adding a first quantity amino acid “Z” activated ester to the first reactor;

transferring the first quantity of amino acid “Z” activated ester to the second reactor;

adding a second quantity of amino acid “Z” activated ester to the first reactor;

removing the first quantity of amino acid “Z” activated ester from the second reactor;

transferring the second quantity of amino acid “Z” activated ester from the first reactor to the second reactor; and

removing the second quantity of amino acid “Z” activated ester from the second reactor.

12. The process of claim 11, further comprising:

adding the first additional quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first additional quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group of amino acid “X” activated ester; and

adding the second additional quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor.

13. The process of claim 12, further comprising:

adding the first quantity of amino acid “Z” activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid “Z” is removed from the second reactor; and

adding the second quantity of amino acid “Z” activated ester to the third reactor, wherein this adding occurs after the second quantity of amino acid “Z” activated ester is removed from the second reactor.

14. The process of claim 1, wherein the peptide synthesis resin in the first and second reactors are Seiber or Rink resins.

15. The process of claim 1, wherein the peptide synthesis resin in the first and second reactors are Wang resins or CTC resins.

16. The process of claim 1, wherein the amount of amino acid X that is added is between 1.1 and 1.6 equivalents.

17. A process for coupling amino acid “X” to a protected N-group that is attached to a peptide synthesis resin found in a first reactor and a second reactor arranged in series, comprising:

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor;

removing the second quantity of de-protecting reagent from the second reactor;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor;

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor; and

removing the second quantity of amino acid “X” activated ester from the second reactor.

18. The process of claim 17, wherein the amino acid “X”, that is found in the first and second quantity of amino acid “X” activated ester, itself has a protected N-group.

19. The process of claim 16 or 17, further comprising:

adding the first quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin;

removing the first quantity of de-protecting reagent from the third reactor;

adding the second quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor;

adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and

transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor;

transferring the third quantity of de-protecting reagent from the second reactor to the third reactor;

adding the first quantity of amino acid “X” activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the second reactor;

removing the first quantity of amino acid “X” activated ester from the third reactor;

adding the second quantity of amino acid “X” activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the third reactor; and

removing the second quantity of amino acid “X” activated ester from the third reactor.

20. The process of claim 19, further comprising:

adding a third quantity amino acid “X” activated ester to the first reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor;

transferring the third quantity of amino acid “X” activated ester to the second reactor, wherein this transferring occurs after the second quantity of amino acid “X” activated ester is removed from the second reactor;

transferring the third quantity of amino acid “X” activated ester and from the second reactor to the third reactor;

removing the third quantity of amino acid “X” activated ester from the third reactor;

adding the first quantity of amino acid “X” activated ester back to first reactor, wherein this adding of the first quantity of amino acid “X” activated ester occurs after the first quantity of amino acid “X” activated ester is removed from the third reactor.

21. A process for coupling amino acid “X” to a de-protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a de-protected N-group attached to a peptide synthesis resin;

adding a first quantity amino acid “X” activated ester to the first reactor;

removing the first quantity amino acid “X” activated ester from the first reactor;

adding the first quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the first quantity of amino acid “X” activated ester is removed from the first reactor;

adding a second quantity of amino acid “X” activated ester to the first reactor;

removing the first quantity of amino acid “X” activated ester from the second reactor;

removing the second quantity of amino acid “X” activated ester from the first reactor;

adding the second quantity of amino acid “X” activated ester to the second reactor, wherein this adding occurs after the second quantity of amino acid “X” activated ester is removed from the first reactor; and

removing the second quantity of amino acid “X” activated ester from the second reactor.

22. The process of claim 21, further comprising washing the first reactor and a second reactor with solvent.

23. The process of claim 20 or 21, further comprising:

adding the first quantity of amino acid “X” activated ester to a third reactor, wherein this adding occurs after the first quantity of amino acid “X” is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin;

removing the first quantity of amino acid “X” activated ester from the third reacto;r and

adding the second quantity of amino acid “X” to the third reactor.

24. The process of claim 23, further comprising:

adding a third quantity of amino acid “X” to the first reactor, wherein this third quantity of amino acid “X” is added to the first reactor after the second quantity of amino acid “X” has been removed from the first reactor; and

transferring the third quantity of amino acid “X” from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of amino acid “X” is removed from the second reactor.

25. The process of claim 24, further comprising:

removing the second quantity of amino acid “X” from the third reactor;

transferring the third quantity of amino acid “X” from the second reactor to the third reactor;

removing the third quantity of amino acid “X” from the third reactor; and

adding the first quantity of amino acid “X” back to the first reactor, wherein the first quantity of amino acid “X” is added back to the first reactor after the first quantity of amino acid “X” de-protecting reagent has been removed from the third reactor.

26. A process for de-protecting a protected N-group attached to a peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second reactor being arranged in series and each containing a quantity of a protected N-group attached to a peptide synthesis resin;

adding a first quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the first reactor

adding the first quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the first reactor;

adding a second quantity of de-protecting reagent to the first reactor;

removing the first quantity of de-protecting reagent from the second reactor;

removing the second quantity of de-protecting reagent from the first reactor;

adding the second quantity of de-protecting reagent to the second reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the first reactor; and

removing the second quantity of de-protecting reagent from the second reactor.

27. The process of claim 26, further comprising washing the first reactor and a second reactor with solvent.

28. The process of claim 26 or 27, further comprising:

adding the first quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin;

removing the first quantity of de-protecting reagent from the third reactor; and

adding the second quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor.

29. The process of claim 28, further comprising:

adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and

transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor.

30. The process of claim 29, further comprising:

removing the second quantity of de-protecting reagent from the third reactor;

transferring the third quantity of de-protecting reagent from the second reactor to the third reactor;

removing the third quantity of de-protecting reagent from the third reactor; and

adding the first quantity of de-protecting reagent back to the first reactor, wherein the first quantity of de-protecting reagent is added back to the first reactor after the first quantity of de-protecting reagent has been removed from the third reactor.

31. The process of claim 9, wherein multiple washing cycles occur between the addition of each particular amino acid.

32. The process of claim 31, wherein the washing solvent from each washing cycle is collected in a recycle vessel and this recycled washing solvent is used in the next washing cycle.

33. The process of claim 9, wherein the solvent comprises an environmentally friendly or green solvent.

34. The process of claim 33, wherein the environmentally friendly or green solvent is acetonitrile, ethyl acetate, isopropyl acetate, 2-methyltetrahydrofuran, cyclopentyl methyl ether, or N-butylpyrrolidinone, or mixtures thereof.

35. The process of claim 9, wherein the solvent is a mixture of N-butylpyrrolidinone and tetrahydrofuran.

36. The process of claim 9, wherein the solvent is a mixture of N-butylpyrrolidinone and 2-methyltetrahydrofuran.