Oxime Resin

Oxime resin is a synthesis resin compatible with Boc chemistry. Peptides can be cleaved from this resin under basic conditions which leave the side chain and N-terminal protecting groups in place, making this resin very useful for preparing protected peptide fragments that can be used in the segment condensation synthesis of larger peptides.

This resin is also useful for preparing structural analogs which differ only at the C-terminal. By using different alkyl amines to displace the peptide from the resin, a series of N-alkylamides of the same peptide can be prepared. Likewise, using DBU and different alcohols a variety of peptide esters can be prepared. Using acetate salts of amino acid esters produces a series of peptide analogs that differs only in the C-terminal amino acid.

Although this resin is compatible with Boc chemistry, the oxime ester linkage is susceptible to TFA. Therefore the Boc group is removed with 25% TFA in DCM during synthesis and end-capping is performed after each coupling to block any active sites on the resin that may have been exposed. For best results, the peptide should not exceed 10 residues.

Attaching the First Amino Acid

1. In a round bottom flask suspend the resin in DMF (approximately 15 mL per gram of resin).
2. In a separate flask dissolve 1.5 to 2.5 equivalents (relative to the resin) of the Boc-amino acid in a minimum amount of DMF. Add the same equivalency of HOBt. Stir the mixture until the HOBt dissolves. If the HOBt doesn’t dissolve completely, add just enough DMF to bring it into solution. Add this solution to the resin.
3. In a separate flask dissolve 0.1 equivalent (relative to the resin) of DMAP in a minimum amount of DMF.
4. Add 1.0 equivalent (relative to the amino acid) of DIC to the resin mixture then add the DMAP solution. Equip the flask with a drying tube.
5. Agitate the mixture with a mechanical shaker for 2 to 3 hours at room temperature. Add 2 equivalents (relative to the resin) of acetic anhydride and pyridine to the reaction flask and mix an additional 30 minutes at room temperature to end cap any unreacted hydroxyl groups on the resin.
6. Remove a small sample of the resin and wash it with DCM. Test for free amino groups using the Kaiser test. If there are free amino groups, add 1 equivalent of acetic anhydride and pyridine to the reaction flask and mix for 30 minutes.

7. Filter the resin in a fine porosity sintered glass funnel and wash it 3 times with DMF, then 3 times with DCM, and finally 3 times with methanol. In each wash use enough solvent to slurry the resin. After the final methanol wash, dry the resin in vacuo to a constant weight. The substitution of the resin can be estimated from the weight gain of the resin. For a more accurate determination of the resin substitution, a picric acid test should be performed.

Cleavage to Protected Peptide Acid

1. Suspend the resin in 95:5 THF/H₂O (v/v).
2. Add 2 equivalents of DBU and shake the mixture mechanically for 4 hours.
3. Filter the resin and wash it several times with DCM and methanol.
4. Combine the filtrates and evaporate to dryness.
5. Dissolve the residue in DCM and wash it twice with 1N HCl.
6. Dry the DCM layer over drying agent then evaporate to yield the crude protected peptide.

Cleavage to Protected Peptide Ester

1. Suspend the resin in the alcohol or 95:5 THF/alcohol (v/v).
2. Add 2 equivalents of DBU and shake the mixture mechanically for 2 hours.
3. Filter the resin and wash it several times with DCM and methanol.
4. Combine the filtrates and evaporate to dryness.
5. Dissolve the residue in DCM and wash it twice with 1N HCl.
6. Dry the DCM layer over drying agent, then evaporate to yield the crude protected peptide.

Cleavage to Protected Peptide Amides

1. Add a solution (60 mL/100 mg of resin) of ammonia in 50% (v/v) THF/methanol saturated at 0°C. Seal the flask and set it aside in a fume hood at room temperature for 16 hours.
2. In a fume hood, filter the resin and wash it with methanol. Evaporate the combined filtrates to obtain the crude peptide amide.

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