Selective Removal of Mtt Protecting Group From Amines

Methyltrityl (Mtt) is utilized to protect the sidechain amine groups of lysine, ornithine, 2,4-diaminobutyric acid, and 2,3-diaminopropionic acid. It can be selectively removed under mild conditions to allow further modification of peptides on resin at the side chains of these amino acids. Mtt can be removed with 1-2% trifluoroacetic acid (TFA) in dichloromethane (DCM) containing triisopropylsilane to prevent reattachment of the trityl group, or with triethylsilane (TES) in hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE). On hydrophobic resins Mtt can even be removed with acetic acid (AcOH)/TFE/DCM 1:2:97 (v:v:v). On hydrophilic resins such as TentaGel resins, Mtt fails to cleave with AcOH/TFE/DCM.¹

Cleavage With TFA/TIS/DCM²

1. Suspend the resin in TFA/TIS/DCM (1:2:97 v:v:v) (approximately 10 mL per gram of resin).
2. Gently shake at room temperature for 30 minutes. Remove a few beads and add 1-2 drops of TFA. If the beads turn orange immediately, continue shaking for another 30 minutes and retest.
3. Filter the resin and wash twice with DCM.
4. Wash the resin twice with methanol (MeOH).
5. Wash the resin twice with DCM.
6. Wash the resin twice with 1% diisopropylamine (DIEA) in N,N-dimethylformamide (DMF).
7. Wash the resin twice with DMF.

The resin is ready for further elaboration.

Cleavage With TES/HFIP/TFE/DCM

1. Suspend the resin in TES/HFIP/TFE/DCM (2:1:0.5:6.5 v/v/v/v) (approximately 10 mL per gram of resin).
2. Gently shake at room temperature for 1 hour. Remove a few beads and add 1-2 drops of TFA. If the beads turn orange immediately, continue shaking for another hour and retest.
3. Filter the resin and wash twice with DCM.
4. Wash the resin twice with DMF.
5. Wash the resin twice with 10% diisopropylamine (DIEA) in N,N-dimethylformamide (DMF).
6. Wash the resin twice with DMF.

The resin is ready for further elaboration.