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TDBTU (O-3,4-Dihydro-4-oxo-1,2,3-benzotriazine-3-yl-1,1,3,3-tetramethyluronium tetrafluoroborate)

TDBTU is a coupling reagent that causes very little epimerization. In the coupling of peptide fragments to form SK&F 107647, TDBTU was shown to produce significantly less epimerization than PyBOP, HBTU, HATU, and many other common coupling reagents.¹ TDBTU was utilized in the large scale synthesis of over 2 kg of SK&F 107647.¹

Fragment Coupling¹

1. Dissolve the peptide ester in DMF (N,N-dimethylformamide) (approximately 16 ml per mmol of peptide ester).
2. Add 1.25 equivalents of the N-protected peptide fragment.
3. Cool the solution to -25° C.
4. Add 2.25 equivalents of DIEA (diisopropylethylamine).
5. Add 1.05 equivalents of TDBTU.
6. Stir at -25° C for one hour.
7. Stir overnight at room temperature
8. Pour the mixture into water (10 times the volume of DMF) containing 8% w/w sodium carbonate.
9. Stir for 30 minutes
10. Collect the solid by filtration, wash with water, and dry in vacuo to obtain the crude product.

¹ Hiebl, J, et al. *J. Peptide Res.* **1999**, *54*, 54-65.