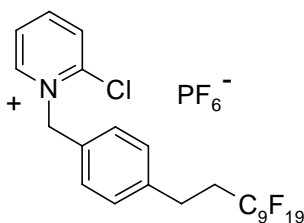


F019099


Rapid Activation of Carboxylic Acids for Amide Formation

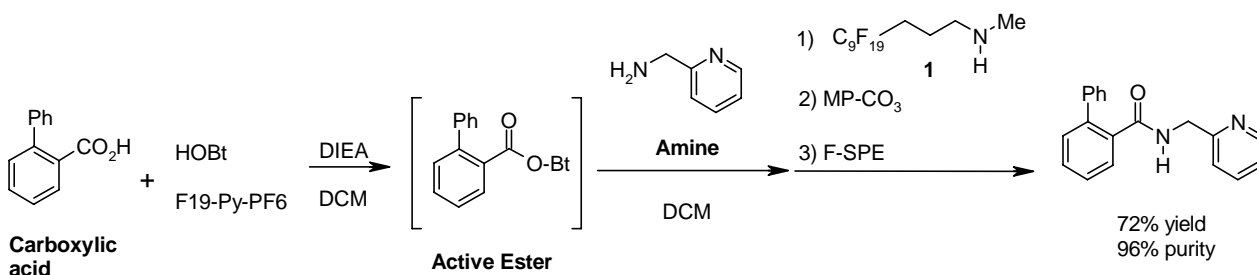
 2-Chloro-1-[4-(1*H*,1*H*,2*H*,2*H*-perfluoroundecyl)benzyl]-pyridinium hexafluorophosphate

Chemical Formula: C₂₃H₁₄ClF₂₅NP
 Abbreviation: F19-Py-PF6
 Formula Weight: 845.75
 Appearance: White Powder
 Melting Point: 174–178 °C
 Stability: Can be handled in air

Why Fluorous? 2-Halopyridinium salts (Mukaiyama's condensation reagents) are effective reagents for activation of carboxylic acids to form esters, amides, and lactones.¹ For example, *N*-ethyl-2-halopyridinium tetrafluoroborate is an excellent coupling reagent with 1-hydroxy-7-azabenzotriazole (HOAt) in peptide synthesis² that gives results superior to other commonly used coupling reagents such as PyBroP. These reagents may be underutilized because they form the corresponding *N*-alkylpyridones, and removal of the pyridone typically requires chromatography. The fluorous pyridinium salt keeps the same high reactivity as the parent. At the same time, it provides simple and quick removal of the pyridinium salt and its pyridone by fluorous solid-phase extraction (F-SPE) making the isolation of the desired product much easier. The fluorous pyridinium salt is especially useful with 1-hydroxybenzotriazole (HOBt) to form OBt esters from various carboxylic acids. Activation of a carboxylic acid is rapid, and is typically complete in less than 5 minutes. This active ester is then reacted with amine to form the corresponding amide.

TYPICAL PROCEDURES: Amide Coupling³

- With Non Aqueous Workup:** The following procedure includes scavenging of excess OBt ester intermediate with fluorous amine **1** and uses resin-bound carbonate (MP-CO₃, Argonaut Technologies) to remove HOBt and also to neutralize HCl and HPF₆ salts from *N,N*-diisopropylethylamine (DIEA). Filtration followed by F-SPE gives the desired coupling products.

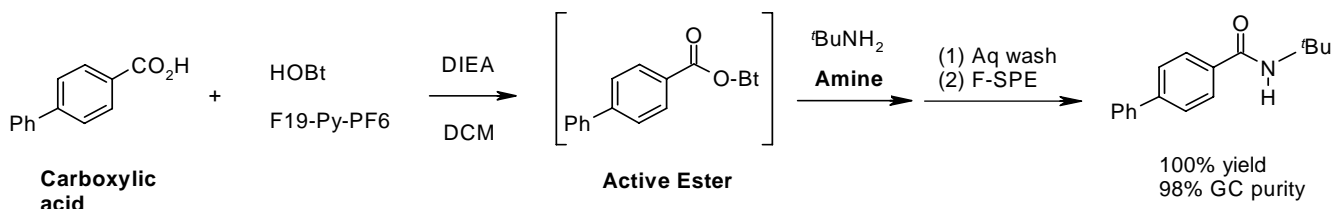

Materials Needed

Materials Needed	Quantity
Carboxylic acid	48 mg, 0.24 mmol
Amine	22 mg, 0.20 mmol
DCM (dry)	1 mL, 0.5 mL, 0.5 mL
Fluorous Amine 1	46 mg, 0.09 mmol
MP-CO ₃	1.14 g, 2.9 mmol/g
FluoroFlash® SPE cartridge	1 x 5 g
MeOH:H ₂ O (80:20)	12 mL
HOBt	40 mg, 0.29 mmol
F19-Py-PF6	227 mg, 0.27 mmol
DIEA	0.14 mL, 0.78 mmol

Stepwise Procedure:

- Mix carboxylic acid, HOBt, and F19-Py-PF6 in dichloromethane (DCM, 1 mL);
- Add DIEA, and stir for 5 min or until the solution becomes clear;
- Add amine in DCM (0.5 mL), and stir until the amine is consumed;
- Add fluorous amine **1** in DCM (0.5 mL);
- Add MP-CO₃, and stir vigorously for 2 h;
- Rinse the resin with DCM (3 x 2 mL), and concentrate the filtrate;
- Take up residue in DCM (1 mL), and charge to the F-SPE cartridge;
- Elute cartridge with MeOH:H₂O, and concentrate eluent to give 42.3 mg (72% yield) of product.

2. **With Aqueous Workup**³: In the following example, a slight excess of amine is used to consume all the active ester. HOBt and DIEA salts are effectively removed by aqueous NaHCO₃ wash, and the reaction mixture in DCM is directly charged to an F-SPE cartridge. The excess amine and DIEA are removed under vacuum. If non-volatile amine is used, then we recommend using the fluoros isocyanate (Catalog Number F017032) to scavenge the amine prior to the aqueous wash.


Materials Needed
Quantity
Stepwise Procedure:

Carboxylic acid	19 mg, 0.10 mmol
HOBt	17 mg, 0.12 mmol
F19-Py-PF ₆	101 mg, 0.12 mmol
DIEA	0.07 mL, 0.36 mmol
Amine	10.5 mg, 0.14 mmol
DCM (dry)	0.4 mL, 1.0 mL
Aqueous NaHCO ₃	15 mL
FluoroFlash® SPE cartridge	1 x 5 g
MeOH:H ₂ O (80:20)	12 mL

- 1) Mix carboxylic acid, HOBt, and F19-Py-PF₆ in DCM (0.4 mL);
- 2) Add DIEA, and stir for 5 min;
- 3) Add amine in DCM (1 mL), stir until the active ester is consumed;
- 4) Wash the reaction mixture with saturated aqueous NaHCO₃ (3 x 5 mL);
- 5) Charge the DCM layer to the F-SPE cartridge;
- 6) Elute cartridge with MeOH:H₂O and concentrate the eluent to give 26 mg (100% yield) of the product.

Insider Tips:

- The formation of OBt active ester is exothermic. On larger scale, it is recommended to cool the reaction mixture in an ice-water bath prior to the addition of DIEA.
- Recommended reaction solvents are DCM and THF. The pyridinium salt reacts with DMF.
- Excess OBt ester can also be removed by MP-trisamine (Argonaut Technologies). Add MP-CO₃ and MP-Trisamine when the coupling step is completed.
- Loading solvents and volumes affect the reliability of the F-SPE in predictable ways. For a 5 g F-SPE cartridge, 1 mL or less of DCM is recommended. In case the coupling product is insoluble in 1 mL of DCM, addition of DMF to the DCM mixture is recommended to dissolve the coupling product. Also, be sure to read the application note on "Fluorous Solid-Phase Extractions" if you are new to this technique.
- Typically the spent F-SPE cartridge retains an orange color at the top; however, it can be reused by washing with THF, then reconditioning according to the F-SPE application note.
- In the absence of HOBt, a significant amount of carboxylic anhydride forms. However, the acyloxy-pyridinium intermediate has typically much higher reactivity than its corresponding OBt active ester. If the acylation reaction is very slow, it is recommended to run a reaction without HOBt. Use MP-Trisamine (Argonaut Technologies) to remove carboxylic anhydride.

REFERENCES:

1. Mukaiyama, T. 'New Synthetic Reactions Based on the Onium Salts of Aza-Arenes' *Angew. Chem. Int. Ed.* **1979**, *18*, 707. and references there in.
2. Li, P.; Xu, J.-C. '1-Ethyl 2-Halopyridinium Salts, Highly Efficient Coupling Reagents for Hindered Peptide Synthesis both in Solution and the Solid-Phase' *Tetrahedron* **2000**, *56*, 8119.
3. Nagashima, T.; Petro, M.; Lu, Y.; Zhang, W. 'Fluorous 2-chloropyridinium salt (Mukaiyama condensation reagent) for amide formation reactions' *Tetrahedron Lett.* **2005**, *46*, 6585.