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USE OF PENTAFLUOROPHENYL ESTERS FOR ONE-POT PROTECTION/ACTIVATION OF AMINO AND THIOL CARBOXYLIC ACIDS

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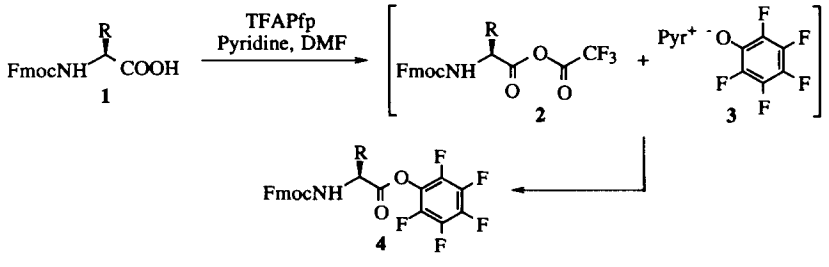
Abstract. As part of our efforts in the area of combinatorial chemistry, we have been exploring new methods for the construction of combinatorial libraries in a bidirectional fashion. Herein, we describe a new one-pot procedure for the simultaneous protection/activation of amino and thiol carboxylic acids using pentafluorophenyl trifluoroacetate (TFAPfp) and related pentafluorophenyl reagents (FmocPfp and AcPfp). Copyright © 1996 Elsevier Science Ltd

Amino carboxylic acids are frequently used as building blocks or templates in the construction of both peptide and organic combinatorial libraries.[1] However, their use is limited by the need for the protection/deprotection of the amino and carboxylic acid functionalities.

One protecting group that has been used extensively in the area of solid-phase peptide chemistry is the pentafluorophenyl ester.[2] Treatment of N-protected amino acids with pentafluorophenyl esters under mild conditions results in the formation of activated building blocks that can be used to form internal or external amides. One reagent, pentafluorophenyl trifluoroacetate (TFAPfp) has been shown to be particularly useful in preparing activated carboxylic acids via a mixed anhydride type of intermediate (Scheme 1).[3] Others have shown that Pfp esters can also be used to protect amines as the corresponding acyl derivatives.[4]

SCHEME 1

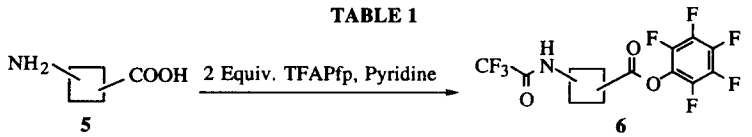


As part of our program aimed toward the construction of novel and diverse combinatorial libraries, we examined the use of pentafluorophenyl trifluoroacetate and related compounds as reagents for the simultaneous protection/activation of amino carboxylic acids. If templates containing amines and carboxylic acids could be

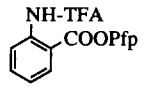
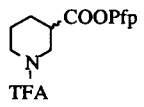
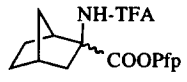
protected and activated in one step, it would facilitate the construction of diverse chemical entities. Herein, we report our work using Pfp esters for the simultaneous protection and activation of amino carboxylic acid templates.

We first examined the use of TFAPfp as shown in Table 1. We have found that treatment of amino carboxylic acids with 2 equivalents of TFAPfp in either THF or DMF at room temperature provides the trifluoroacetyl-protected, pentafluorophenol-activated derivative **6** in good yields and high purity.[5] This procedure is applicable to a variety of compounds which include aryl-, cyclic- and aliphatic amino carboxylic acids. All reaction products are washed with dilute aqueous acid and base solutions, providing the Pfp products as solids. The crude products can be chromatographed over silica gel or directly recrystallized from hexanes/ethyl acetate to >97% purity.

TABLE 1



5 **6**

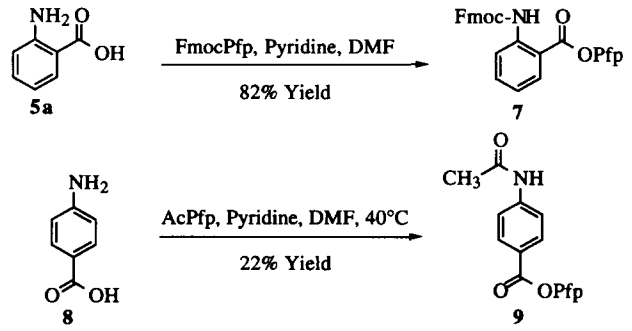
Pfp Ester **6**		Solvent	Yield	Purity*	m.p.(°C)
6a		THF DMF	62% 92%	>99%	41-42
6b		THF DMF	52% 89%	>99%	41-43
6c		DMF	83%	>99%	119-120
6d	TFA-(L)-Alanine-OPfp	THF DMF	87% 76%	>98%	78-79
6e	TFA-Glycine-OPfp	DMF	88%	>98%	60-61
6f	TFA-(L)-Ala-(L)-Phe-OPfp	DMF	83%	>97%	146-147

*Purities of the products were determined by HPLC after recrystallization.

To further explore this chemistry, we examined the use of other acyl pentafluorophenyl reagents. Treatment of **5a** with 6 equivalents of 9-fluorenylmethylpentafluorophenyl carbonate (Fmoc-Pfp) produced the Fmoc-protected aminocarboxylate derivative **7** in an 82% yield (Scheme 2). This procedure provides an Fmoc-protected carboxy-activated amino acid, a useful procedure in peptide chemistry that previously took several steps to complete. Treatment of **8** with pentafluorophenyl acetate gave the N-acetyl protected carboxylic acid activated derivative **9** (22% yield). Although the yield of this transformation is low, it does demonstrate that through the use of different pentafluorophenyl acyl derivatives, it is possible to very easily build diverse molecules and structures from common templates. Current studies are aimed at evaluating the scope of this chemistry.

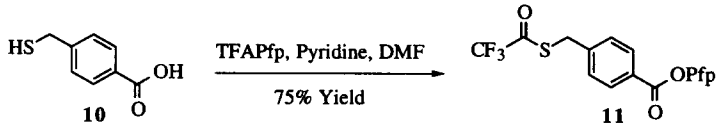
Thus far we have only discussed the protection of an amino carboxylic acid template. Other templates such as thiol carboxylic acids are also useful as combinatorial building blocks. Treatment of 4-(thiomethyl) benzoic acid[6] **10** with pentafluorophenyl trifluoroacetate in a mixture of pyridine/DMF provides the thioacyl amide **11** (75% yield, Scheme 3), further illustrating the potential utility of acyl Pfp derivatives in the protection/activation of thiol carboxylic acids.

SCHEME 2



This new one-pot procedure for the simultaneous protection/activation of amino/thiol carboxylic acids is a favorable alternative to traditional methods of sequential protection and deprotection. We have found that TFAPfp offers both convenience and flexibility to amino carboxylic acid chemistry making this reagent useful for generating combinatorial libraries. Currently, we are in the process of evaluating these reactions further and applying them to the generation of libraries for lead optimization.[7] We are also exploring the use of these reagents in conjunction with solid-phase chemistry for the generation of novel libraries for lead discovery.

SCHEME 3



References and Notes

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5. **General Procedure for the Preparation of Compounds 6**: A solution of the amino carboxylic acid (10 mmol), TFAPfp (20 mmol) and pyridine (20 mmol) in DMF (10 mL) or THF (25 mL) is stirred at room temperature overnight. The reaction mixture is concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with 0.1 N aqueous HCl, followed by aqueous $NaHCO_3$ (5%), and brine (each 3 X 15 mL). The EtOAc layer is dried ($MgSO_4$), filtered and concentrated. Column chromatography (SiO_2, hexanes/EtOAc) or recrystallization of the crude solid using hexanes/EtOAc (appx. 5:1) or hexanes/CH_2Cl_2 (appx. 5:1) provides the Pfp ester **6** as a crystalline white solid. Yields and melting points are reported in Table 1.

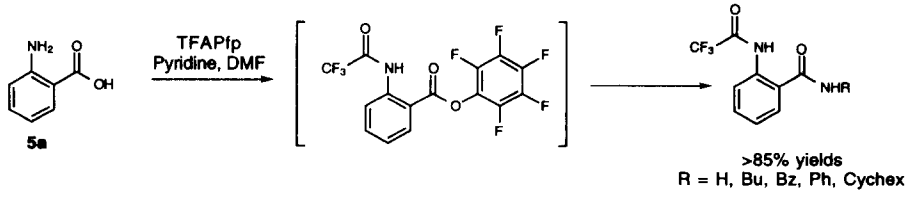
   Pentafluorophenyl 2-(N-Fmoc-amino)benzoate **7**: A solution of the 2-aminobenzoic acid (0.10 g, 0.73 mmol), FmocOPfp (1.8 g, 4.4 mmol) and pyridine (0.18 mL, 2.2 mmol) in DMF (3 mL) is stirred at room temperature for 2 days. The reaction mixture is then concentrated, purified by column chromatography (SiO_2, hexanes/EtOAc, 4:1; then 1:1) and recrystallized from hexanes/$CHCl_3$ to provide the Pfp ester **7** (0.31 g) in 82% yield; ^{1}HNMR ($CDCl_3$) δ 10.11 (s, 1H), 8.56 (d, 1H), 8.30 (dd, 1H), 7.77 (d, 2H), 7.64 (m, 1H), 7.62 (d, 2H), 7.44 (m ,4H), 7.21 (t, 1H), 4.47 (d, 2H), 4.30 (t, 1H); m.p 162-164 °C.

   Pentafluorophenyl 2-(N-acylamino)benzoate **9**: A solution of the 4-aminobenzoic acid (0.20 g, 1.5 mmol), AcOPfp (1.0 g, 4.4 mmol) and pyridine (0.35 mL, 4.4 mmol) in DMF (3 mL) is stirred at 40°C for 2 days. The reaction mixture is then concentrated, purified by column chromatography (SiO_2, hexanes/EtOAc, 4:1; then 1:1) and recrystallized from hexanes/$CHCl_3$ to provide the Pfp ester **9** (0.11 g) in 22% yield; ^{1}HNMR ($CDCl_3$) δ 8.15 (d, 2H), 7.71 (d, 2H), 7.50 (s, 1H), 2.25 (s, 3H); m.p. 124-126 °C.

   Pentafluorophenyl 4-(methyltrifluoroacylthioamide)benzoate **11**: A solution of 4-(thiomethyl)benzoic acid (0.50 g, 3.0 mmol), PfpOTFA (4.2 g, 14.9 mmol) and pyridine (1.2 mL, 14.9 mmol) in DMF (5 mL) is stirred at room temperature for 2 days and worked up as described for compounds **6**, providing compound **11** (0.96 g) in 75% yield; ^{1}HNMR ($CDCl_3$) δ 8.17 (d, 2H), 7.25 (d, 2H), 4.35 (s, 2H)); m.p 47-49 °C.

6. Daines, R. A., Chambers, P. A., Drake, S. E., Foley, J. J., Griswold, D. E., Haltiwanger, R. C., Jakas, D. R., Kingsbury, W. D., Martin, L. D., Pendrak, I., Schmidt, D. B., Tzimas, M. N., Sarau, H. M. *J. Med. Chem.*, **1994**, *37*, 3327.

7. A demonstration of the utility of this chemistry for preparing diverse structures from a common intermediate is as follows: Treatment of **5a** with TFAPfp in pyridine/DMF provides the corresponding N-TFA protected pentafluorophenyl ester. The crude reaction was then divided into 5 equal portions and each was treated with a different amine (NH_3, $nBuNH_2$, $BzNH_2$, $PHNH_2$, piperidine) to provide the corresponding N-trifluoroacetyl amides in >85% yields after aqueous workup.



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