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Simultaneous Protection and Activation of Amino Acids Using Propargyl Pentafluorophenyl Carbonate

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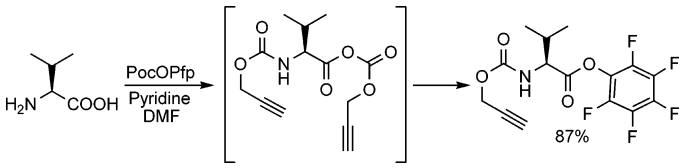
ABSTRACT



A very efficient method for the simultaneous protection of the amino group and activation of the carboxyl group of amino acids is reported using propargyl pentafluorophenyl carbonate (PocOPfp). The amino group is protected as a propargyloxycarbonyl (Poc) derivative, and the carboxyl group is activated as a pentafluorophenyl ester. The yields obtained are good to excellent ranging from 60 to 87%.

The most important steps involved in peptide synthesis are protection of the α-amino group and activation of the α-carboxylic acid group. The efficiency and simplicity of peptide synthesis relies on the strategies employed in achieving these two steps. The most commonly used strategies in peptide synthesis involve protection of the α-amino group in an early step, activation of the carboxylic acid group, and coupling with the amino group of the subsequent amino acid in a later step. Protection of the amino acids is usually done by converting them to carbamates, and the carboxylic acid groups are activated either during the coupling step using various coupling reagents or in a different step as an active ester. Pentafluorophenyl esters, prepared from the carboxylic acids and pentafluorophenol using DCC or EDC, are the most common active esters used in this regard.[1] It is a definite advantage over existing strategies, if protection and activation of amino acids can be achieved in the same step. Suto and Gayo[2] have studied the possibilities of simultaneous protection and activation of amino and thiol carboxylic acids using trifluoroacetyl pentafluorophenolate (TFAOPfp). They could achieve good yields in the protection of amino group as a trifluoroacetamide and the activation of carboxylic acid group as a pentafluorophenyl ester. Their efforts to use 9-fluorenylmethylpentafluorophenyl carbonate (FmocOPfp) for simultaneous protection and activation was limited to just one substrate, *o*-aminobenzoic acid, and was not advantageous, requiring 6 equiv of the reagent. Rao and co-workers[3] have studied the use of *N*-trifluoroacetoxysuccinimide (TFAOSu) for simultaneous protection and activation of amino acids. Though they have reported good yields, their study is limited to unnatural amino acids, which are soluble in a mixture of dichloromethane and pyridine and required 6 equiv of the reagent. Thus, the two available reports on simultaneous protection and activation of amino acids are limited to a few unnatural amino acids, and the protection of the amino group is achieved by converting it to a trifluoroacetamide, which is seldom used in standard peptide synthesis protocols.

An earlier report from our laboratory has shown that propargyl pentafluorophenyl carbonate (PocOPfp, **1**) can be

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(1) Bodanszky, M. *Principles of Peptide Synthesis*, 2nd ed.; Springer-Verlag: Berlin, 1993.

(2) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1996**, *37*, 4915.

(3) Rao, T. S.; Nampalli, S.; Sekher, P.; Kumar, S. *Tetrahedron Lett.* **2002**, *43*, 7793.

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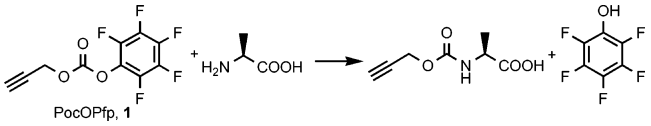
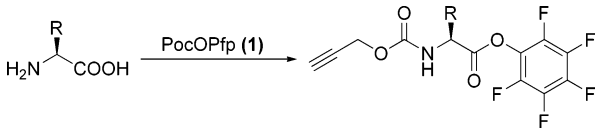
used as an efficient reagent for the protection of amino acids as their propargyl carbamates (Scheme 1).[4]

Scheme 1. Poc Protection of Amino Acids Using PocOPfp



The propargyloxycarbonyl group (Poc), which can be cleaved using benzyltriethylammonium tetrathiomolybdate **2**, has been shown to be an excellent protecting group for amines, and its application in solution-phase peptide synthesis is documented.[5] The application of *N*-Poc-protected pentafluorophenyl esters of amino acids in peptide coupling has also been addressed.[4] We report here the results of our studies to use 2 equiv of PocOPfp for the simultaneous protection and activation of amino acids yielding a Poc-protected amino group and an activated pentafluorophenyl ester of the carboxylic acid (Scheme 2).

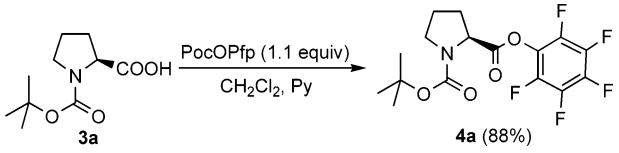
Scheme 2. Simultaneous Protection and Activation of Amino Acids Using PocOPfp



Before attempting simultaneous protection and activation of amino acids, we tried to prepare pentafluorophenyl esters of *N*-protected amino acids using PocOPfp to ensure that PocOPfp can activate carboxylic acids by forming the corresponding pentafluorophenyl esters.

Treating Boc-Pro-OH, **3a**, with PocOPfp (1.1 equiv, 3 h, CH_2Cl_2, pyridine, 0 °C to rt) yielded the corresponding pentafluorophenyl ester **4a** in 88% yield (Scheme 3). We

Scheme 3. Activation of Carboxylic Acid Using PocOPfp



carried out the activation of two other *N*-protected amino acids (**3b**,**c**) using PocOPfp and the corresponding pentafluorophenyl esters (**4b**,**c**) could be obtained in excellent yields

Table 1. Preparation of Pentafluorophenyl Esters Using PocOPfp

entry[a]	*N*-protected amino acids	pentafluorophenyl esters	yield (%)
1	**3a**	**4a**	88
2	**3b**	**4b**	89
3	**3c**	**4c**	85

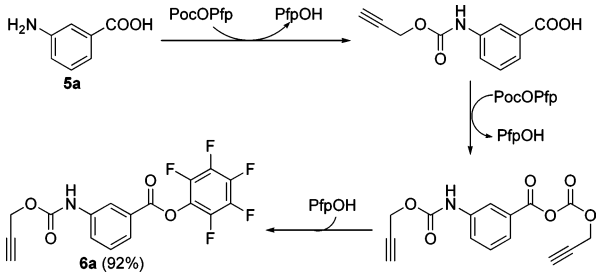
[a] Pyridine (1.1 equiv) was added to a solution of the *N*-protected amino acid dissolved in CH_2Cl_2, PocOPfp (1.2 equiv) was added at 0 °C, the temperature was raised to rt, and the mixture was stirred for 3 h.

(Table 1). Preparation of pentafluorophenyl esters of *N*-protected amino acids using trifluoroacetyl pentafluorophenolate has been reported,[6] and we find that the method using PocOPfp is equally efficient.

Having established that PocOPfp (**1**) can activate carboxylic acids as pentafluorophenyl esters and that **1** is an excellent reagent for the protection of amino groups as Poc derivatives,[4] the simultaneous protection and activation of amino acids with PocOPfp looked feasible.

We initiated our studies with *m*-aminobenzoic acid (**5a**), which on treatment with **1** (2.1 equiv, DMF/pyridine, 3 h, 0 °C to rt) yielded the protected and activated compound **6a** in 92% yield (Scheme 4). *o*-Aminobenzoic acid **5b** under

Scheme 4. Simultaneous Protection and Activation of *m*-Aminobenzoic Acid with PocOPfp



the same reaction conditions afforded the *N*-protected and *C*-activated compound **6b** in 90% yield (Table 2). Encouraged by this success, this methodology was extended to a number of natural α-amino acids. Accordingly, when L-leucine **5c** was treated with PocOPfp in the presence of pyridine in DMF, **6c** was isolated in 82% yield (Scheme 5).

The results of *N*-protection and *C*-activation of a number of amino acids with **1** are summarized in Table 2. The yields were very good, ranging from 60% to 87% (Table 2).

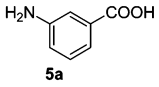
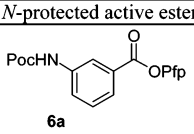
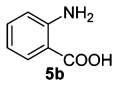
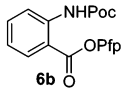
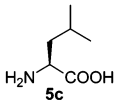
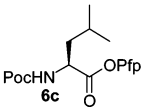
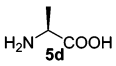
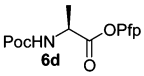
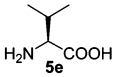
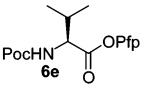
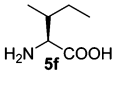
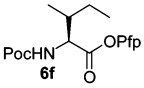
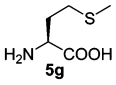
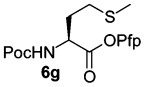
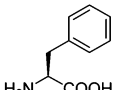
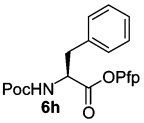
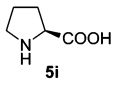
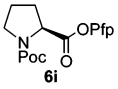
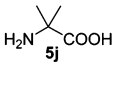
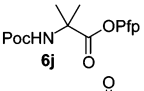
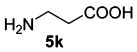
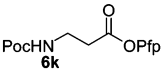
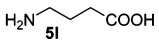
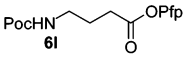
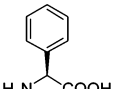
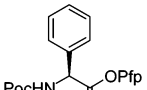
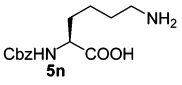
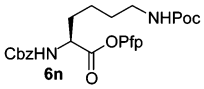
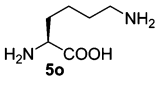
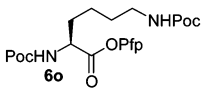
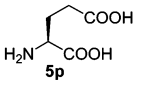
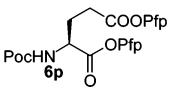
It was interesting to note that α-amino acids having alkyl side chains yielded the *N*-protected active esters in better

(4) Bhat, R. G.; Kerouredan, E.; Porheil, E.; Chandrasekaran, S. *Tetrahedron Lett.* **2002**, *43*, 2467.

(5) Bhat, R. G.; Sinha, S.; Chandrasekaran, S. *Chem. Commun.* **2002**, 812.

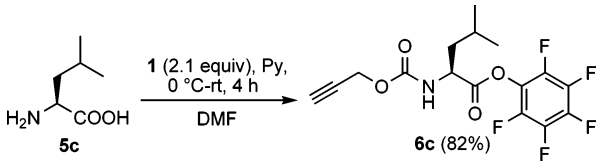
(6) Green, M.; Berman, J. *Tetrahedron Lett.* **1990**, *31*, 5851.

Table 2. Simultaneous Protection and Activation of Amino Acids Using PocOPfp

entry[a]	amino acids	*N*-protected active esters	yield (%)
1	 **5a**	 **6a**	92
2	 **5b**	 **6b**	90
3	 **5c**	 **6c**	82
4	 **5d**	 **6d**	68
5	 **5e**	 **6e**	87
6	 **5f**	 **6f**	84
7	 **5g**	 **6g**	72
8	 **5h**	 **6h**	73
9	 **5i**	 **6i**	77
10	 **5j**	 **6j**	76
11	 **5k**	 **6k**	60
12	 **5l**	 **6l**	68
13	 **5m**	 **6m**	75
14	 **5n**	 **6n**	76
15[b]	 **5o**	 **6o**	57
16[b]	 **5p**	 **6p**	62

[a] Except where otherwise noted, PocOPfp (2.1 equiv) was added to a suspension of the amino acid and pyridine (2.1 equiv) in DMF at 0 °C and the reaction mixture was allowed to attain room temperature and stirred for 3−5 h. [b] 3.1 equiv of PocOPfp and pyridine were used.

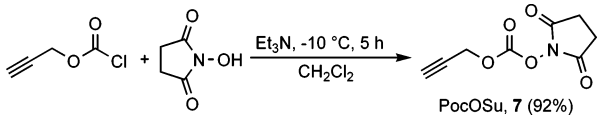
Scheme 5. Simultaneous Protection and Activation of L-Leucine with PocOPfp



yield than other amino acids (entries 3−6, 9, 10). Surprisingly, the yield of Poc-Ala-OPfp (**6d**) was lower than that of Poc-Leu-OPfp (**6c**), Poc-Val-OPfp (**6e**), and Poc-Ile-OPfp (**6f**). Most interestingly and quite surprisingly, the more hindered aminoisobutyric acid (**5j**) yielded Poc-Aib-OPfp (**6j**) in 76% yield. The reaction of unnatural amino acids 3-aminopropanoic (**5k**) and 4-aminobutyric acid (**5l**) and L-phenylglycine (**5m**) under these conditions with **1** yielded the corresponding *N*-protected active esters in 60%, 68%, and 75% yields, respectively. When α-amino-protected lysine (**5n**) was used for the reaction, the fully protected active ester Cbz-Lys(Poc)-OPfp (**6n**) was obtained in 76% yield. Reaction of lysine (**5o**) with 3.1 equiv of **1** afforded the fully protected active ester Poc-Lys(Poc)-OPfp (**6o**) in 57% yield. Similarly, when glutamic acid (**5p**) was treated with 3.1 equiv of **1**, the *N*-protected active diester Poc-Glu(Pfp)-OPfp (**6p**) was obtained in 62% yield. The optical rotation values of the pentafluorophenyl esters were found to match with the values for those prepared previously[4] in two steps, suggesting that there is no racemization during the simultaneous protection and activation.

The success with PocOPfp on the simultaneous protection and activation of amino acids prompted us to study a similar application of *N*-propargyloxycarbonyloxysuccinimide, PocOSu (**7**). PocOSu was prepared by treating *N*-hydroxysuccinimide with PocCl in the presence of triethylamine (Scheme 6).

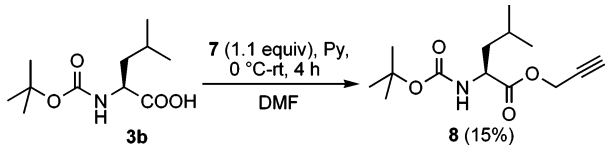
Scheme 6. Preparation of PocOSu



As with PocOPfp, we initially attempted to prepare *N*-succinimidyl active esters of *N*-protected amino acids using PocOSu (**7**). Treating Boc-Leu-OH (**3b**) with 1.1 equiv of **7** did not give the expected active ester; instead, the corresponding propargyl ester **8** was isolated in 15% yield after 24 h (Scheme 7). Though the formation of **8** was unexpected, it was not surprising as the esterification of carboxylic acids using chloroformates in the presence of a base is well documented.[7] We believe that, in this case, PocOSu acts more like propargyl chloroformate and results in the formation of the propargyl ester of **3b** rather than the expected active ester.

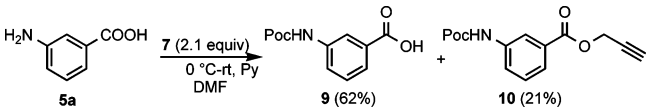
(7) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560.

Scheme 7. Reaction of PocOSu with Boc-Leu-OH



Reaction of *m*-aminobenzoic acid **5a** with 2.1 equiv of PocOSu in the presence of pyridine yielded only the *N*-protected carboxylic acid **9** and the propargyl ester **10** instead of the expected *N*-protected active ester after 24 h (Scheme 8). These observations suggest that while PocOPfp can be used successfully for simultaneous protection and activation of amino acids, PocOSu (**7**) is not useful to achieve the same goal.

Scheme 8. Reaction of PocOSu with *m*-Aminobenzoic Acid



In conclusion, we have developed a very effective methodology for the simultaneous protection and activation of α-amino acids using PocOPfp (**1**). The method described here is better than all the previously reported methods as it allows the protection of amino group as a propargyloxycarbonyl (Poc) derivative, which can be deprotected using **2**, and has found its place as an amino protecting group in peptide synthesis. The products are obtained in good to excellent yields. The protection and activation of amino acids containing more than one amino or carboxylic acid groups are also possible. However, efforts toward extending this methodology using PocOSu (**7**) were unsuccessful.

Acknowledgment. R.R. thanks CSIR, New Delhi, for a Senior Research Fellowship.

Supporting Information Available: Full experimental details, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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