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Synthesis and applications of propargyl pentafluorophenyl carbonate for peptide synthesis

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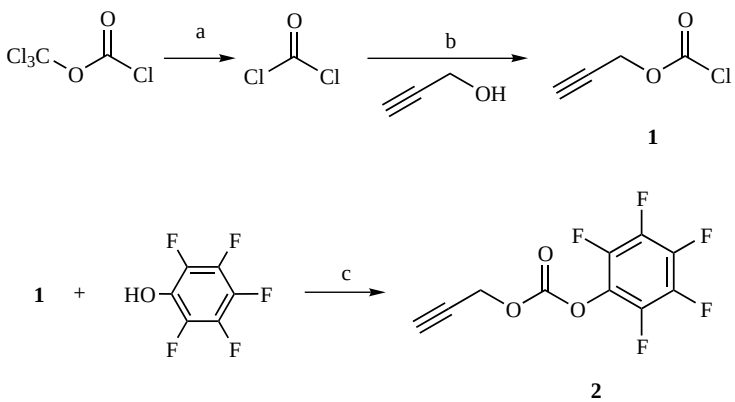
Abstract—Propargyl pentafluorophenyl carbonate was synthesised in quantitative yield by the reaction of propargyl chloroformate and pentafluorophenol. All the *N*-propargyloxycarbonyl (*N*-Poc) amino acids were obtained in good yield. The use of Poc-OPfp in peptide synthesis has been explored. © 2002 Elsevier Science Ltd. All rights reserved.

A number of protective groups have been developed for the amino group for peptide and protein synthesis. However, the development of more satisfactory protective groups and more effective methods for protection and cleavage are still important in organic synthetic methodology. The tempting possibility to build chains by linking amino acids or peptides to each other and to continue the build-up without isolation of intermediates attracts wide interest. To prevent side reactions like double acylation, either acidic additives such as 1-hydroxybenzotriazole[1] or else highly reactive pentafluorophenyl esters are used.[2,3] In the last few years the *N*-fluorenylmethoxycarbonyl (Fmoc) protective group has become a useful tool for peptide chemistry. As the Fmoc group is sensitive to mild base, premature deblocking leading to multiple acylations is a major drawback to its use. Schön and Kisfaludy have introduced and shown the utility of Fmoc-OPfp in peptide synthesis[4] and since then it has been extensively used for the synthesis of glycopeptides.

Earlier work from our laboratory has shown the efficiency of the propargyloxycarbonyl (Poc) group as a new protecting group for alcohols, phenols as well as amines and amino acids. The protective group was selectively cleaved by benzyltriethylammonium tetrathiomolybdate [$(PhCH_2NEt_3)_2MoS_4$] under mild and neutral conditions.[5,6]



Scheme 1. *Reagents and conditions*: (a) Et_2O, C (activated), 0°C, 7 h. (b) Et_2O, 0°C, 12 h. (c) NEt_3, Et_2O, 0°C, 7 h.

Keywords: amino acids; peptide synthesis; protecting groups; propargyl pentafluorophenyl carbonate; tetrathiomolybdate.

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Results of this work led us to explore the use of *N*-Poc amino acids for peptide synthesis via the activation of the carboxylic group using pentafluorophenol. Here, we wish to report the synthesis of propargyl pentafluorophenyl carbonate (Poc-OPfp) **2** and its utility in peptide synthesis. Poc amino acids and the synthesis of dipeptides have been achieved by the use of propargyl pentafluorophenyl carbonate **2**. The reagent, Poc-OPfp, **2** can be easily synthesised under mild conditions from propargyl chloroformate (Poc-Cl) **1**.[7] It is a stable crystalline solid[8] (Scheme 1) obtained in almost quantitative yield and is better than Fmoc-OPfp in terms of thermal stability and reactivity.[9]

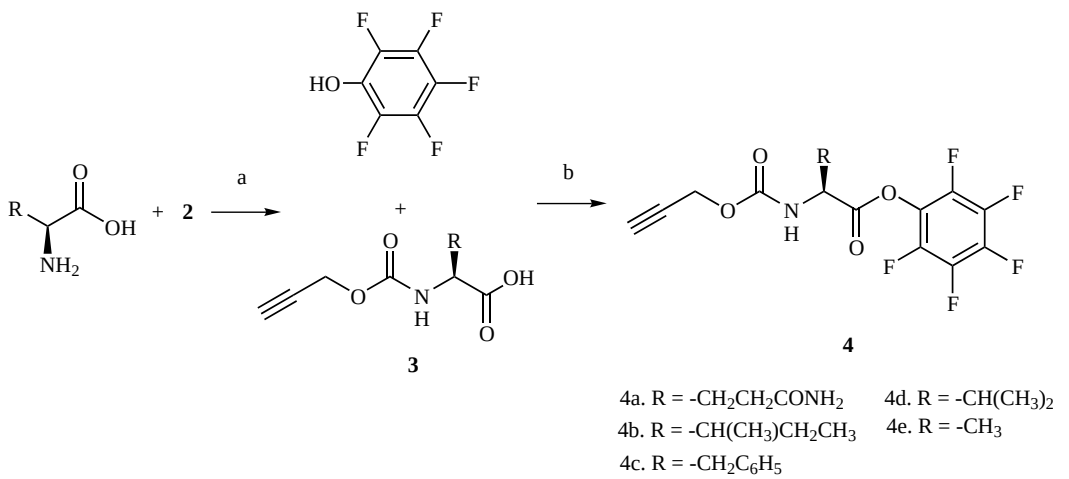
A number of *N*-Poc amino acids **3** were synthesised in very good yields (76–93%) by the addition of the reagent, Poc-OPfp, **2** to the corresponding amino acids as a suspension in sodium hydrogen carbonate in H_2O/acetone/DMF at −10°C (Table 1). Generally low yields were obtained if the reactions were carried out at room temperature (60–66%).

The *N*-Poc amino acid pentafluorophenyl esters **4** were prepared in excellent yields by the addition of EDC to the solution of pentafluorophenol and the corresponding *N*-Poc amino acids in acetonitrile at 0°C (Scheme 2) (Table 1). In the initial studies, reactions were carried out in two steps so as to characterise the intermediate products. Subsequently it was demonstrated that liberated pentafluorophenol in the first step can be used for the synthesis of **4** in one pot so as to have a rapid continuous process. All the peptides **5**–**8** were synthesised by the addition of **4** to the suspension of amino acid in H_2O/acetone/DMF and sodium hydrogen carbonate (−10°C, 15 min and then at 28°C, 30 min) (Scheme 3) and were obtained in good yields (Table 1).[10] Use of EDC proved to be better as a coupling reagent than DCC in our case as the reaction with DCC entailed a troublesome work-up and low yield. All the peptides were enantiomerically pure by chiral HPLC.[11]

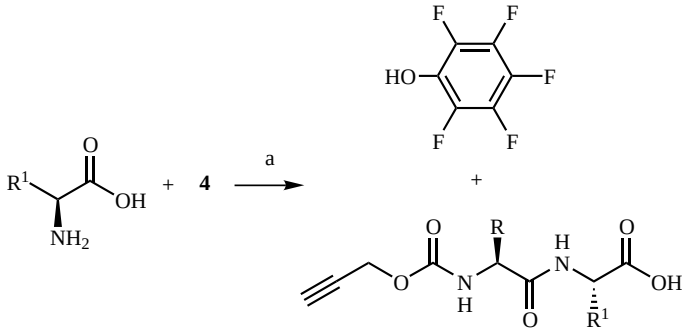
In conclusion, we have introduced propargyl pentafluorophenyl carbonate (Poc-OPfp) as a new reagent for

Table 1.

	Amino acids	*N*-Poc-amino acids (**3**) yield (%)	*N*-Poc-amino acid -Pfp esters (**4**) yield (%)		*N*-Poc peptides (**5**)–(**8**) yield (%)
a.	Gln	84	84	Poc-Ile-Phe-OH (**5**)	95
b.	Ile	83	80	Poc-Phe-Ala-OH (**6**)	89
c.	Phe	89	89	Poc-dl-Phe-Ala-OH (**7**)	90
d.	Val	93	93	Poc-Val-Leu-OH (**8**)	90
e.	Ala	86	90		
f.	Leu	78	–		
g.	Pro	76	–		
h.	Ser	77	–		
i.	dl-Phe	89	90		



Scheme 2. *Reagents and conditions*: (a) H_2O/acetone/DMF, $NaHCO_3$, −10°C, 1 h then rt, 3–16 h. (b) EDC, CH_3CN, 0°C, 1 h then rt, 3 h.



5. R = -CH(CH$_3$)CH$_2$CH$_3$, R^1 = -CH$_2$C$_6$H$_5$

6. R = -CH$_2$C$_6$H$_5$, R^1 = -CH$_3$

7. R = -CH$_2$C$_6$H$_5$ (rac), R^1 = -CH$_3$

8. R = -CH(CH$_3$)$_2$, R^1 = -CH$_2$CH(CH$_3$)$_2$

Scheme 3. *Reagents and conditions*: (a) H_2O/acetone/DMF, $NaHCO_3$, −10°C, 15 min then rt, 30 min.

the preparation of *N*-Poc amino acids and for the convenient synthesis of peptides in excellent yield.

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References

1. Bodanszky, A.; Bodanszky, M.; Chandramouli, N.; Kwei, J. Z.; Martinez, J.; Tolle, J. C. *J. Org. Chem.* **1980**, *45*, 72.
2. Kisfaludy, L.; Roberts, J. E.; Johnson, R. H.; Mayers, G. L.; Kovacs, J. *J. Org. Chem.* **1970**, *35*, 3563.
3. Kisfaludy, L.; Schön, I.; Szirtes, T.; Nyéki, O.; Löw, M. *Tetrahedron Lett.* **1974**, 1785.
4. Schön, I.; Kisfaludy, L. *Synthesis* **1983**, 325.
5. Swamy, V.; Ilankumaran, P.; Chandrasekaran, S. *Synlett* **1997**, 513.
6. Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771.
7. To a solution of propargyl chloroformate (6 g, 4.9 ml, 0.050 mol) and pentafluorophenol (9.2 g, 0.050 mol) in dry diethyl ether (100 ml), triethylamine (7 ml, 0.050 mol) was added dropwise at 0°C. The mixture was stirred for 7 h at 0°C, then washed with water and immediately dried over sodium sulfate. The solvent was removed in vacuo and the crude product was recrystallised from *n*-hexane to give propargyl pentafluorophenyl carbonate (Poc-OPfp) as a white crystalline solid in quantitative yield.
8. Selected data for (**2**): Mp 65–67°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.9 (d, 2H, $J=2.7$ Hz), 2.65 (t, 1H, $J=2.3$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 57.5, 75.3, 77.2, 136.0, 138.3, 139.5, 142.9, 150.8; ^{19}F NMR ($CDCl_3$, 282.2 MHz) δ −153.54 (2F, *o*-F), −157.62 (1F, *p*-F), −162.4 (2F, *m*-F).
9. Schön, I.; Kisfaludy, L. *Synthesis* **1986**, 303.
10. In the present work, peptide synthesis has not been attempted using pentafluorophenyl esters derived from leucine, proline and serine.
11. HPLC was carried out using Chiralcel OD CN:0000CE JH 004, Shimadzu SPD-6A, solvent system 30% isopropanol in *n*-hexane.