New Polymer-Supported Allyloxycarbonyl (Alloc) and Propargyloxycarbonyl (Proc) Amino-Protecting Reagents

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Abstract: New polymer-supported reagents, Alloc-P-OSu and Proc-P-OSu, have been prepared from a polymeric *N*-hydroxysuccinimide (P-HOSu), and used as solid-supported reagents for the allyloxycarbonyl (Alloc) and propargyloxycarbonyl (Proc) protection of the amino group. These new polymeric reagents are safe and stable, the residual P-HOSu generated after the protection reaction can be easily separated by simple filtration and reused.

Key words: amino acids, polymers, protecting reagents, solid-supported reagents

The allyloxycarbonyl (Alloc or Aloc) group shows a growing interest nowadays as a protecting group for primary and secondary amines and especially for amino acids in the synthesis of peptides due to its stability to acidic and some basic conditions, thus allowing selective deprotection of other groups such as Boc or Fmoc.[1] The removal of the Alloc group was originally achieved employing rather inconvenient methods such as the use of metallic sodium in liquid ammonia.[2] However, the development of mild deprotection methods mainly based on the palladium(0)-catalyzed allyl transfer[1] boosted the use of the Alloc protecting group, especially for the synthesis of highly sensitive structures such as glycopeptides.[3] These compounds are crucial components of the oligosaccharide coat in the lipid and protein surface components of cell membranes, and provide the basis for the recognition by the immune system.

In addition, the propargyloxycarbonyl (Proc or Poc) group has appeared recently as an alternative amino protecting group to the Alloc.[4] Thus, the Proc group can also resist acidic and mild basic conditions, but can be cleaved under neutral conditions using benzylammonium tetrathiomolybdate under ultrasonic irradiation,[4a] with Amberlite-bound tetrathiomolybdate,[4d] $Co_2(CO)_8$[4b] and with various other metal reagents.[4c]

The *N*-protection of amines with the Alloc or Proc groups is generally achieved by reaction of the amine with the corresponding chloroformates Alloc-Cl (**1**)[1] or Proc-Cl (**2**).[4a–4d] These reagents are very sensitive to moisture, therefore handling and storage precautions have to be taken and the reagents may contain varying amounts of very toxic phosgene.[5] Furthermore, it has been observed that the use of Alloc-Cl for the *N*-protection of amino acids can induce the formation of protected dipeptide by-products.[1d] Other more stable reagents for the introduction of the Alloc group have been developed, such diallyl dicarbonate (**3**),[6] allyl succinimidyl carbonate (Alloc-OSu, **4**),[7] allyl 1-benzotriazolyl carbonate (Alloc-OBt, **5**)[6,8] and allyl 1-[6-(trifuoromethyl)]benzotriazolyl carbonate (**6**).[9] In addition, the Proc group has also been introduced using propargyl pentafluorophenyl carbonate (Proc-OPfp, **7**).[4e] Recently, the polymer-supported Alloc-protecting reagent Alloc-OBt-6-carboxamidomethyl polystyrene (**8**) has been commercialized (Figure 1).[10]

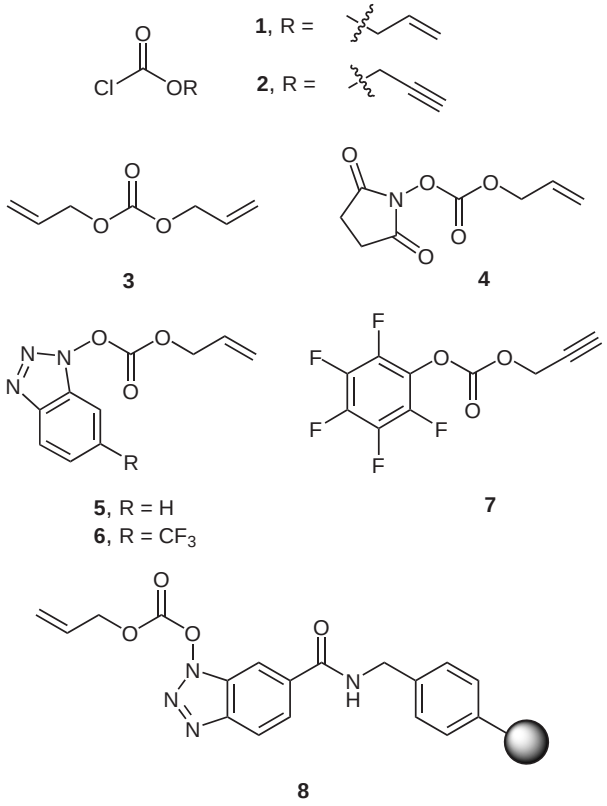

Figure 1

Amongst all the safer and more convenient alternatives to Alloc-Cl (**1**) or Proc-Cl (**2**), probably Alloc-OSu (**4**) and its non-described counterpart Proc-OSu are the more promising from an economical point of view. These reagents would be even more valuable if an easy separation of the liberated *N*-hydroxysuccinimide (HOSu) from the

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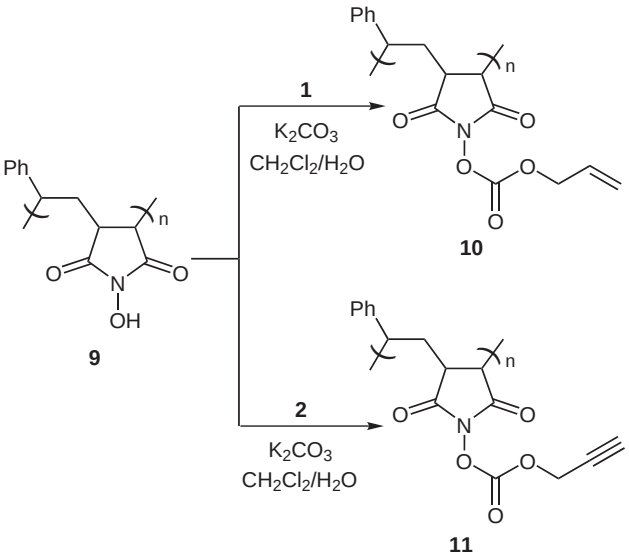
protected substrate could be achieved, a feature especially interesting when working on a small scale. In this respect, and with attention to the growing interest in the development of polymer-supported reagents for organic synthesis,[11] our group has recently reported the facile preparation of an economical reagent which incorporates the *N*-hydroxysuccinimide moiety into a polymer.[12] This polymeric HOSu (P-HOSu, **9**) has been employed as a solid supported racemization-lowering additive for DCC-mediated peptide formation.[12] In addition, P-HOSu (**9**) has also been used for the preparation of reagents for the protection of amino groups with the 9-fluorenylmethoxycarbonyl (Fmoc)[13] or 2,7-di-*tert*-butyl-9-fluorenylmethoxycarbonyl (Dtb-Fmoc)[14] groups. Furthermore, ammonium salts obtained from P-HOSu (**9**) have been employed as amino releasing and racemization-lowering reagents in carbodiimide-mediated amidations.[15] In all cases, these polymeric reagents are rather soluble in polar organic solvents and the P-HOSu (**9**) can be easily removed from the reaction mixture by simple filtration and reused. Using these precedents, we envisaged that P-HOSu (**9**) could be suitable for the preparation of new advantageous and economical polymer-supported reagents for the Alloc- and Proc-*N*-protection of amino acids related to Alloc-OSu (**4**) and its propargylic counterpart Proc-OSu.

Polymer-supported Alloc-OSu (Alloc-P-OSu, **10**) was prepared by reaction of P-HOSu (**9**)[16] with allyl chloroformate (**1**) using triethylamine as organic base in dichloromethane as solvent (Scheme 1). The related polymeric Proc-OSu (Proc-P-OSu, **11**) was prepared from P-HOSu (**9**) and propargyl chloroformate (**2**) using the same methodology (Scheme 1). The polymers Alloc-P-OSu (**10**) and Proc-P-OSu (**11**) were isolated as white solids and showed two strong C=O stretching IR bands at 1785 cm^{-1} and 1735 cm^{-1}, whereas the starting P-HOSu presented only a C=O band at 1707 cm^{-1}. In addition, polymer **11** showed a new IR stretching band at 2134 cm^{-1}, typical of a carbon-carbon triple bond. These reagents proved to be very stable, no appreciable decomposition or loss of effectiveness being observed after storage for months at room temperature without any special precautions.

The polymers Alloc-P-OSu (**10**) and Proc-P-OSu (**11**) prepared as shown were employed as solid-supported Alloc- and Proc-protecting reagents for the amino group of different substrates. Thus, amines, free amino acids or amino acid esters reacted with **10** or **11** in the presence of triethylamine using refluxing dichloromethane as solvent to give the corresponding crude pure Alloc- or Proc-protected derivatives in good yields (62–98%), after filtration and work-up (Table 1), even with hindered systems such as aminoisobutyric acid (Table 1, entries 7 and 13). The filtered solid was washed with 2 M HCl allowing the quantitative recovery of P-HOSu (**9**), which was recycled for the preparation of new polymeric reagents **10** and **11**.



Scheme 1

Table 1 Alloc and Proc-*N*-protected Amines and Amino Acids Using **10** and **11**

Entry	Product	Reagent	Yield (%)[a,b]	$[\alpha]_D^{25c,d}$
1	AllocNH^{n}Bu	**10**	76	
2	AllocAlaOH	**10**	77	–19
3	Alloc-ValOH	**10**	72	–10
4	AllocPheOH	**10**	80	–9
5	AllocPheOEt	**10**	88	–15
6	AllocPheOBn	**10**	98	–12
7	AllocAibOH	**10**	75	
8	ProcNH^{n}Bu	**11**	76	
9	ProcAlaOH	**11**	75	–25
10	ProcValOH	**11**	70	–21
11	ProcPheOH	**11**	71	–20
12	ProcPheOBn	**11**	87	–18
13	ProcAibOH	**11**	62	

[a] All compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, MS).
[b] Isolated pure compounds (^1H, ^{13}C NMR) after filtration and aqueous work up.
[c] For crude products.
[d] *c* 1, EtOH.

In order to compare the results obtained with the polymeric Alloc-protecting reagent **10** with other reagents normally used, we performed the protection reaction of Phe-OH using the toxic chloroformate **1** under the typical Schötten–Baumann reaction conditions,[2] the isolated yield was found to be higher (95%). In addition, when we

prepared Alloc-OSu (**4**) from *N*-hydroxysuccinimide and the chloroformate **1**,[7] and used the product for the protection of the same amino-acid, the isolated yield of Alloc-Phe-OH was 92%, whereas when the carbonate **3** was used for protection the yield was 94%. In general, somewhat higher yields and faster reaction times were obtained using non-polymeric reagents, whereas good results were obtained compared to the polymer-supported reagent **8**. Thus, when the commercial polymeric reagent **8** was employed for the Alloc-protection of Phe-OH under the typical reaction conditions used for **10**, only a 52% yield was obtained, rising to 60% isolated yield when 2 equivalent of **8** were employed. Moreover, we also performed the Alloc-protection reaction of Phe-OBn using Alloc-P-OSu (**10**) and obtained the corresponding Alloc-Phe-OBn in practically quantitative yield (Table 1, entry 6) whereas only a 76% yield is reported when using the polystyrene-bound reagent **8**.[10]

We also compared the performance of the polymeric reagent **11** in the Proc-protection of Phe-OH with the corresponding chloroformate **2**, which afforded a 90% yield of Proc-Phe-OH. In addition, we prepared Proc-OSu in 93% yield from *N*-hydroxysuccinimide and the chloroformate **2** following the same reported procedure as for Alloc-OSu (**4**),[7] its use affording a 90% yield of Proc-Phe-OH.

We conclude that Alloc-P-OSu (**10**) and Proc-P-OSu (**11**) are new safe, stable and efficient economical solid supported reagents for the Alloc- and Proc-protection of the amino group. The use of these polymeric reagents presents the advantage that, compared to other reagents currently employed, of the easy separation and recycling of the P-HOSu (**9**) liberated after the protection reaction. The results obtained are better than those obtained using currently available and more expensive solid-supported Alloc-protecting reagents.[17]

Procedure for the Synthesis of Polymeric Reagents Alloc-P-OSu (10) and Proc-P-OSu (11)[17]

A mixture of P-HOSu[16] (**9**) (4 g, 4 mmol) and K_2CO_3 (1.1 g, 8 mmol) in water (30 mL) was stirred at room temperature for 30 min. A solution of allyl chloroformate (**1**) (1.75 mL, 16 mmol) or propargyl chloroformate (**2**) (1.62 mL, 16 mmol) in acetone (30 mL) was added and the resulting suspension was stirred at room temperature for 1 day. Hexane (30 mL) was added and the solid was filtered, washed with a mixture of acetone/water/hexane (10/10/10 mL) and dried in an oven (70 ºC) under vacuum (0.1 Torr) affording 4.2 g of Alloc-P-OSu (**10**) or 4.2 g of Proc-P-OSu (**11**).

Procedure for the Alloc- or Proc-*N*-protection Using 10 or 11

To a suspension of Alloc-P-OSu (**10**) (400 mg, 0.4 mmol) or Proc-P-OSu (**11**) (400 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) was added a solution of the corresponding free amino acid (0.4 mmol) and K_2CO_3 (39 mg, 0.4 mmol) in water (15 mL). The mixture was stirred under reflux for 1 day and the solvents were evaporated (15 Torr). The resulting solid was suspended in water (20 mL) and filtered. The solid consisted of HOSu (**9**), which was quantitatively recovered after washing with 2 M HCl. The filtrate was acidified with concd HCl and extracted with AcOEt (3 × 20 mL). The organics layers were dried (Na_2SO_4) and evaporated (15 Torr) affording pure Alloc- or Proc-amino acids. In the case of the *N*-protection of amines, to the suspension of **10** or **11** in CH_2Cl_2 was added the corresponding amine (0.4 mmol) and the mixture was stirred at 40 ºC for 1 day. The solid was filtered off and the filtrate was evaporated (15 Torr) affording the pure *N*-protected amine.

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References

(1) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; J. Wiley & Sons: New York, **1999**, 526–528. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**, 199–202. (c) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer: Berlin, **1984**. (d) Albericio, F. *Biopolymers (Peptide Science)* **2000**, *55*, 123.

(2) Stevens, C. M.; Watanabe, R. *J. Am. Chem. Soc.* **1950**, *72*, 725.

(3) Some examples: (a) Paulsen, H.; Merz, G.; Brockhausen, I. *Liebigs Ann. Chem.* **1990**, 719. (b) Attal, S.; Bay, S.; Cantacuzene, D. *Tetrahedron* **1992**, *48*, 9251. (c) Unverzagt, C.; Kunz, H. *Bioorg. Med. Chem.* **1994**, *2*, 1189. (d) Meinjohanns, E.; Vargas-Berenguel, A.; Meldal, M.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2165.

(4) (a) Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771. (b) Fukase, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron Lett.* **1999**, *40*, 1169. (c) Fukase, Y.; Fukase, K.; Kusumoto, S. *Pept. Sci.* **1999**, *36*, 93. (d) Bhat, R. G.; Sinha, S.; Chandrasekaran, S. *Chem. Commun.* **2002**, 812. (e) Bhat, R. G.; Kérourédan, E.; Porhiel, E.; Chandrasekaran, S. *Tetrahedron Lett.* **2002**, *43*, 2467.

(5) Herrinton, P. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd.: Chichester, **1995**, 95–96.

(6) Sennyey, G.; Barcelo, G.; Senet, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5811.

(7) Blaakmeer, J.; Tijsse-Klasen, T.; Tesser, G. I. *Int. J. Pept. Protein Res.* **1991**, *37*, 556.

(8) Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400.

(9) Takeda, K.; Tsuboyama, K.; Hoshino, M.; Kishino, M.; Ogua, H. *Synthesis* **1987**, 557.

(10) Novabiochem (2002/3 catalogue: 5 g, 162).

(11) For recent reviews on polymer-supported chemistry see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (d) Brown, R. *Contemp. Org. Synth.* **1997**, 216. (e) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (f) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (g) Lorsbach, B. A.; Kurth, M. J.; Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (h) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817. (i) Wenworth, R. Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (j) Brown, A. R. *Chem. Rev.* **1999**,

99, 1549. (k) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (l) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035. (m) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (n) Orain, D.; Ellard, J.; Bradley, M. *J. Comb. Chem.* **2002**, *4*, 1.

(12) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2001**, *42*, 4487.

(13) (a) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2001**, *42*, 7579. (b) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M.; Yus, M. ES P200101169, **2001**.

(14) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1817.

(15) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2003**, *44*, 463.

(16) The loading of P-HOSu(**9**) was 1.0 mmol/g, as it was determined by the assay of the OH group content: Dendrinos, K. G.; Jeong, J.; Huang, W.; Kalivretenos, A. G. *Chem. Commun.* **1998**, 499.

(17) Available from MEDALCHEMY S. L.