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Solid-phase synthesis of 4-aminopiperidine analogues using the Alloc protecting group: an investigation of Alloc removal from secondary amines†

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Abstract—A useful method for Alloc removal from secondary amines on solid-phase has been optimised. The use of $Me_2NH{\cdot}BH_3$ (40 equiv., 40 min) as scavenger of the allyl cations in a palladium-catalysed process with $Pd[PPh_3]_4$ leads to quantitative removal of the Alloc group without any allyl back alkylation. Other scavengers such as morpholine or $PhSiH_3$ are clearly inferior. Furthermore, this study has highlighted differences in the reaction kinetics of the deprotection step between secondary and primary amines such as those from α-amino acids.

In the area of combinatorial chemistry and solid-phase synthesis, there is a constant need for new methods that easily introduce and cleanly remove protecting groups.[1] Since the 4-aminopiperidine substructure is central to a variety of drug-like molecules,[2] our group was interested in developing an efficient and reliable solid-phase synthesis for the preparation of libraries of 4-aminopiperidine derivatives. One of the main concerns with the synthetic approach selected was the choice of a suitable protecting group for the secondary amine function of the 4-aminopiperidine building block. Initially, the use of 4-amino-1-Fmoc-piperidine as a building block was planned, as Fmoc is compatible with major synthetic strategies used in solid-phase and can be removed easily under mild basic conditions.[3] However, its synthesis in reasonable yield failed, probably due to incompatibility between the free amino function and the Fmoc group. As an alternative to the Fmoc group, various examples of the protection of amines using the allyloxycarbonyl (Alloc) group have been described.[4] However, use of the Alloc protecting group in solid-phase synthesis for secondary amines like piperidine has not been reported before.[5] Secondary amines are more nucleophilic than primary amines and are therefore more prone to suffer allyl back alkylation, the main drawback of the use of allyl based protecting groups.[4]

We present here the results obtained using 4-amino-1-Alloc-piperidine (**1**) for the solid-phase synthesis of the 4-aminopiperidine amide analogues (**3**) and the deprotection conditions explored for removal of the allylic carbamate whilst avoiding the formation of the allylamine derivative and other by-products. Our synthetic strategy was (i) attachment of 4-amino-1-Alloc-piperidine to a BAL linker[6] derivatised resin through a reductive amination; (ii) acylation of the secondary amine thus obtained with a carboxylic acid; (iii) removal of the Alloc group; (iv) derivatisation via the amino function of piperidine, and (v) cleavage from the resin (Scheme 1).

4-Amino-1-Alloc-piperidine (**1**) was obtained in two steps in good yield starting from the piperidone, as outlined in Scheme 2.[7]

The choice of an appropriate allyl scavenger is clearly the key factor in establishing a general and convenient strategy for the removal of Alloc groups from primary, and, more importantly, secondary amines. In the literature several protocols using a large variety of nucle-

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† Abbreviations used: BAL, backbone amide linker, specifically as implemented in the tris(alkoxy)benzylamide system; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; NDMBA, *N*,*N*′-dimethyl barbituric acid.

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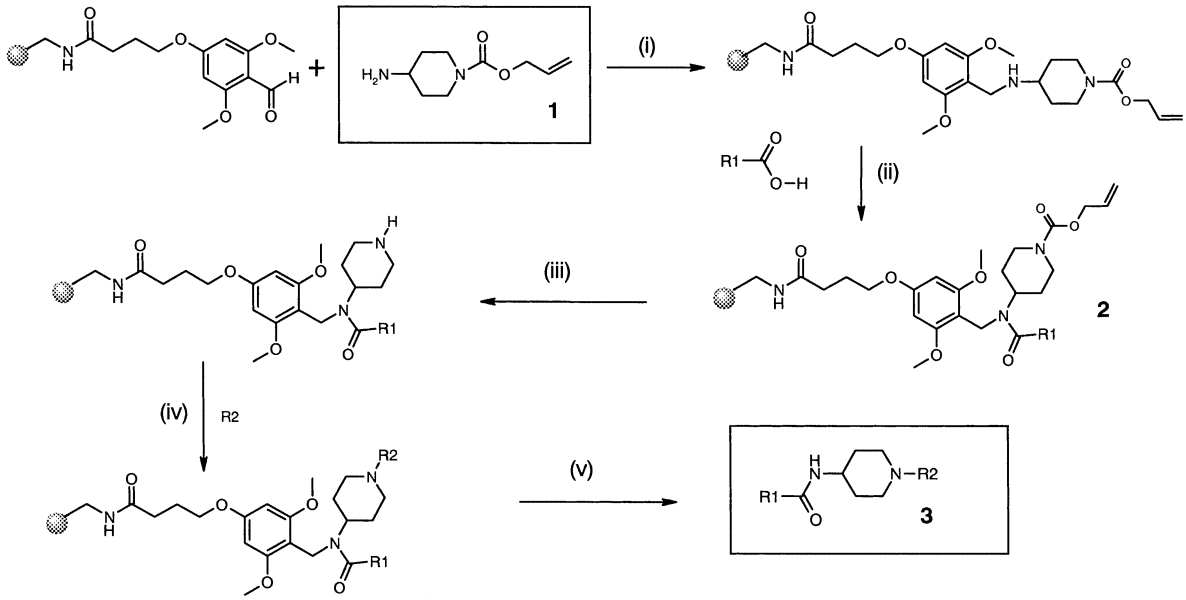
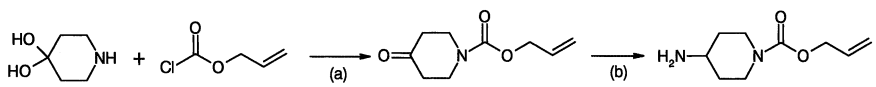


Scheme 1. *Reagents and conditions*: (i) $NaBH_3CN$, DMF–DCM (8:2), 18 h, rt; (ii) HATU, DIEA, DMF–DCM (1:9), 2 h, rt; (iii) see Table 1; (v) TFA–CH_2Cl_2 (1:1).



Scheme 2. *Reagents*: (a) H_2O, K_2CO_3; (b) $NaBH_3CN$, NH_4OAc, MeOH.[8]

ophilic species with soluble palladium catalyst have been described.[4] In order to test some different procedures, biphenyl-2-carboxylic acid piperidin-4-ylamide was synthesised by acylation of the 4-amino-1-Alloc-piperidine anchored to the BAL-resin with the *o*-phenylbenzoic acid, followed by removal of the Alloc group, and cleavage from the resin before further reaction with R2 containing reagents (Scheme 1). The products obtained were analysed by HPLC–MS.

In the first deprotection experiment catalysed with $Pd[PPh_3]_4$, the hydride donor $PhSiH_3$ was chosen as a neutral and easy to handle allyl group scavenger.[9] After treatment of the resin **2** with 20 equiv. of $PhSiH_3$ and 0.1 equiv. of $Pd[PPh_3]_4$ (2×10 min, see Ref. 10 for experimental details), only 52% of the expected NH piperidine was obtained, while 42% of the allyl piperidine derivative was detected together with 6% of another impurity, which initially we ignored. Although some back alkylation (maximum of 5%) has been reported in the deprotection of *N*-Alloc-*N*-methylbenzylamine in solution where 2 equiv. of $PhSiH_3$ were used,[4] the amount of the allylpiperidine derivative obtained in this solid-phase approach, where a 20-fold excess of scavenger was used, was quite unexpected. It was apparent that a careful systematic approach was required in order to optimise the reaction conditions.

For this systematic study, an initial set of experiments (Table 1, entries 1–5) with a small selection of scavengers and two different reaction times (20 and 120 min) was set up. The hydride donor $Me_2NH{\cdot}BH_3$ was selected,[5] as well as the nucleophilic secondary amine morpholine, which is used broadly for cleavage of allyl esters,[11] and finally the carbon nucleophile *N*,*N*′-dimethyl barbituric acid (NDMBA).[12]

The best preliminary results were obtained using 20 equiv. of the amino–borane complex (entry 1) which lead, after 2 h of treatment, to 85% of the deprotected NH-piperidine, while only 7% of the *N*-allylpiperidine analogue was obtained. In the case of morpholine, significant amounts of the desired NH derivative (67%) were only obtained when 5 equiv. of HOAc[13] were added to the 20 equiv. of scavenger (entry 3). In the same experiment a significant amount of *N*-allylated amine was obtained (19%). A large excess of HOAc (entry 4) did not improve the results. On the other hand, with NDMBA (entry 5) only the unchanged 1-Alloc-piperidine derivative was recovered after 2 h of reaction time. In the best two experiments (entries 1 and 3), besides the *N*-allyl product, we detected 10–14% of the same impurity that was initially observed in the $PhSiH_3$ experiment. This was characterised by HPLC–MS, and later confirmed by synthesis as the *N*-formylpiperidine derivative.

It is important to point out that, with regard to reactivity, *N*-Alloc-piperidines seemed to undergo deprotection on solid-phase much more slowly than other allyl carbamates ($Me_2NH{\cdot}BH_3$ has been reported to lead to complete deprotection of *N*-Alloc-amines in less than 10 minutes and NDMBA in less than 90 minutes).[5]

From the above experiments, the amino–borane complex $Me_2NH{\cdot}BH_3$ appeared to be the most suitable

Table 1. Alloc deprotection of 4-aminopiperidine derivatives catalysed by $Pd(PPh_3)_4$

	Scavenger	Additive[13]	% NH		% *N*-Allyl		% *N*-Alloc		% *N*-Formyl	
			20 min	120 min	20 min	120 min	20 min	120 min	20 min	120 min
1	$Me_2NH{\cdot}BH_3$ (20 equiv.)		50	85	7	7	33	1	3	10
2	Morpholine (20 equiv.)		15	41	2	10	78	45	0	2
3	Morpholine (20 equiv.)	HOAc (5 equiv.)	67	67	19	19	0	0	14	14
4	Morpholine (20 equiv.)	HOAc (40 equiv.)	0	9	0	1	100	90	0	1
5	NDMBA (20 equiv.)		0	2	0	0	100	98	0	0
			40 min	120 min	40 min	120 min	40 min	120 min	40 min	120 min
6[a]	$Me_2NH{\cdot}BH_3$ (40 equiv.)		88	88	0	0	0	0	12	12
7	$Me_2NH{\cdot}BH_3$ (20 equiv.) + piperidine (20 equiv.)		81	81	5	5	0	0	14	14
8	$Me_2NH{\cdot}BH_3$ (40 equiv.)	2% H_2O	61	–	30	–	0	–	9	–
9	$NaBH_3CN$ (40 equiv.)	1% HOAc	54	54	0	0	36	36	2	2

[a] This experiment has been repeated with freshly distilled DMF after the preparation of this manuscript: 99% of NH product was obtained and less than 1% of *N*-formyl was detected.

scavenger, although back alkylation still occurred to a significant extent. To improve the yield of the deprotection step, a second set of experiments was carried out with this hydride donor, trying different reaction conditions and also testing the pseudometallic hydride $NaBH_3CN$ (entries 6–9).

Results illustrated in Table 1 (entry 6) show that using a 40-fold excess of $Me_2NH{\cdot}BH_3$ eliminates the competing side-reaction leading to allylation. The excess of nucleophile also improved the reaction rate leading to complete deprotection of the allyl carbamate in 40 minutes. The presence of water (entry 8) was detrimental, favouring the back alkylation. Furthermore, the combination of the hydride and piperidine (entry 7), which could compete with the piperidine bound to the resin, did not totally eliminate the side reaction. Finally, although $NaBH_3CN$ (entry 9) was very effective as a scavenger in preventing the back alkylation, the kinetics of deprotection were slower than for $Me_2NH{\cdot}BH_3$ and the crude product displayed more impurities by HPLC.

In order to compare results with the reportedly more efficient but toxic tributyltin hydride,[14] the deprotection experiment was repeated using the same conditions as in entry 1 but with $n Bu_3SnH$ (20 equiv.) instead of $Me_2NH{\cdot}BH_3$. After 20 minutes of reaction time, results equivalent to using 40 equiv. of $Me_2NH{\cdot}BH_3$ (entry 6) were obtained. Nevertheless, in both cases 12% of the formyl derivative was observed. Despite these promising results the use of tributyltin hydride was avoided mainly because of its toxicity.

In conclusion, a useful method for Alloc removal from secondary amines in solid-phase has been optimised. The use of $Me_2NH{\cdot}BH_3$ (40 equiv., 40 min) as scavenger of the allyl cations in a palladium-catalysed deprotection process with $Pd[PPh_3]_4$ leads to quantitative removal of the Alloc group without any allyl back alkylation. Other scavengers such as morpholine or $PhSiH_3$ give clearly inferior results. The formation of *N*-formyl derivatives seems to be related to the removal step and/or the work-up rather than to the stability of the Alloc derivative, as the quantity of this side product correlates with the yield of deprotected amine. *This undesired side reaction has been practically avoided (<1%) subsequently by using freshly distilled DMF in the work-up procedure*. Furthermore, this study has highlighted differences in reaction kinetics of the deprotection step between the secondary amines described herein and primary amines such as those from α-amino acids.

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7. ***N-Alloc-4-piperidone***. Allyl chloroformate (21 mL, 1.5 equiv.) was added to a solution of 4-piperidone monohydrate hydrochloride (20 g, 0.13 mol) and K_2CO_3 (27 g, 1.5 equiv.) in water (300 mL) at 5°C, and the reaction mixture was allowed to stir for 1 h at 5°C and for another additional hour at rt. The aqueous solution was saturated with NaCl and extracted with diethyl ether (4×100 mL). The combined organic phases were initially washed with a cold 5% aqueous NH_3 solution and brine, dried over $MgSO_4$, and evaporated to dryness to give the title product (23.7 g, quantitative yield), which was used without further purification.
8. ***4-Amino-N-Alloc-piperidine***. A solution of the above ketone (10 g, 0.05 mol), $NaBH_3CN$ (24 g, 7.6 equiv.) and ammonium acetate (42 g, 10 equiv.) in dry methanol (500 mL) was heated under reflux for 1 h. Methanol was removed by evaporation and the residue suspended in 300 mL of H_2O. The solution was acidified with 2N HCl to pH 2 (**caution, HCN evolution!!**), left to stand 15 min with agitation and washed with EtOAc (2×100 mL). The aqueous layer was saturated with K_2CO_3 and extracted with EtOAc (3×100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to dryness to give the title product (7.2 g, 78% yield), which was shown to be pure by ^1H NMR.
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10. *General procedure for Alloc removal*: In a typical experiment, resin **2** (50 mg, 0.05 mmol) was swelled with CH_2Cl_2 (4×30 s) and a 1 or 2 M solution of scavenger (20 or 40 equiv.) in CH_2Cl_2 (for $NaBH_3CN$ experiments, THF was used as a solvent) was first added under an Ar atmosphere and stirred for 5 min. Then, a 0.01 M solution of $Pd[PPh_3]_4$ (0.1 equiv.) in CH_2Cl_2 was added and the resin was allowed to stir. After 10, 20 or 60 minutes, depending on the experiment, the solution was drained off, the resin washed with CH_2Cl_2 (4×30 s) and the deprotection procedure was repeated once. Finally, the resin was washed successively with CH_2Cl_2 (4×30 s), DMF (4×30 s), dioxane–water (9:1) (3×1 min), MeOH (4×1 min), DMF (4×30 s) and CH_2Cl_2 (4×30 s).
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