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Practical Palladium-Mediated Deprotective Method of Allyloxycarbonyl in Aqueous Media

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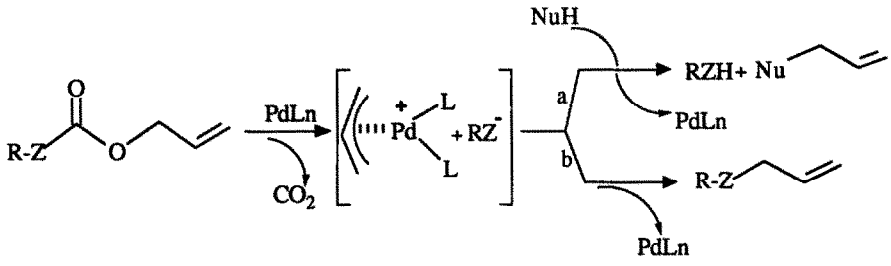
Abstract : The Allyloxycarbonyl (Alloc) moiety can be removed smoothly and selectively in good yield (73-100%) from allylic esters, carbamates and carbonates by aqueous Pd (0) catalyzed allyl transfer to diethylamine in aqueous media employing a water soluble phosphine. The allyl scavenger as well as by product allyl diethylamine are volatile and easily removed in vacuo. In a two phase system an increased selectivity is seen. The method has been successfully used for deprotection of a wide range of secondary amines or base sensitive derivatives and the catalyst is efficiently recycled.

Introduction

The allyloxycarbonyl (Alloc) protective group for hydroxyl, carboxylic and amino functions has been shown to be very useful in organic synthesis.[1] Various methods for the deprotection of the alloc moiety have been developed in which cleavage involves palladium catalyzed reactions under anhydrous conditions.

The deprotection is carried out in the presence of several allyl scavengers formic acid,[2] potassium 2-ethylhexanoate,[3] morpholine, dimedone[4] and tributyltin hydride.[5] However, deprotection of allyl carbamates was limited to primary amines or bulky secondary amines. Allylamine formation is observed due to attack of the free amino group, instead of trapping agent on the π-allyl intermediate (scheme, path b). Although recent progress has been made in the cleavage of the allyloxy carbamate derived from secondary amines using silylated amines,[6] as allyl group scavenger, a simple and unexpensive method would be of great interest. Recently, we found that the water soluble catalytic system $Pd(OAc)_2$ / TPPTS[7] was an efficient catalyst for various palladium cross-coupling reaction in aqueous media.[8] We have also developed new methods for deprotection of allyloxycarbonyl group using nitrogen[9] and sulfur

nucleophiles.[10] In these deprotection procedures the undesired competitive side reaction (path b) observed in deprotection of allyloxy carbamates derived from secondary amines is suppressed.



This paper outlines a method for the deprotection of alloc of hydroxyl and amino functions with water soluble palladium catalyst.[11] This palladium-mediated deprotection of allyloxycarbonyl proceeds with high yields and remarkable regeneration of the parent molecules. In addition an increase of selectivity is seen when the reaction is carried out in a two phase system, and the deprotected products are easily separated from the catalyst which can be recycled.

Discussion

The results are summarized in tables I and II. In the reaction of alloc-protected primary alcohols, regeneration of (R) citronellol from the corresponding carbonate occured upon exposure to $Pd(OAc)_2$ / TPPTS catalytic system in CH_3CN / H_2O in the presence of formic acid or diethylamine as allyl scavengers.

The deprotection with formic acid afforded moderate yield (entry 2). However the reaction is remarkably fast with diethylamine (table I entries 1, 3). Under biphasic conditions CH_2Cl_2 / H_2O / $HNEt_2$ the reaction occured with significant decrease of chemical yield (entry 3). The methyl-2,3-dibenzyl-α-L-glucopyranoside reacted equally well on treatement with $HNEt_2$ (2.2 eq.) at room temperature in 20 min. (entry 4). The deprotection proceeded smoothly with alloc-secondary alcohols (entries 5, 6). Using these best conditions the catalyst was easily recycled (10 times) in the deprotection of alloc-menthol according to the scheme shown in the experimental section. When deprotection of the compound possessing O-isopropylidene groups was conducted in the presence of $Pd(OAc)_2$ / TPPTS / $HNEt_2$ the alcohol was recovered in excellent yield (entry 7). The present procedure is also used to deprotect allyl group from carboxylic acid of base sensitive penem ester. The free carboxylic acid was obtained in high yield and almost pure form, since the by-product allyl diethylamine as well as the amine scavenger used in excess are volatile and removed in vacuo (entry 8).

Based on these results, we attempted to prove the usefulness of this method for cleavage of carbamates of primary and secondary amines. The N-alloc protecting group of primary amines was also cleaved rapidely under our standard conditions (CH_3CN / H_2O) in quantitative yield (table II entries 1, 3). Under biphasic conditions using butyronitrile/water as solvent deprotection of alloc benzylamine was slower again in quantitative yield (entry 2). In the reaction of N-alloc protected cephem, regeneration of the primary amine occured upon exposure to $Pd(OAc)_2$ / TPPTS catalyst in CH_3CN / MeOH / H_2O in the presence of 2.2 eq. of diethylamine. The base sensitive penem was recovered in 73% yield.

Table I : Palladium Mediated Deprotection of Alcohols with $Pd(OAc)_2$ / TPPTS, Et_2NH.

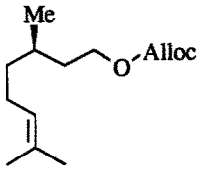
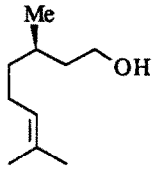
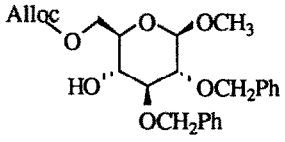
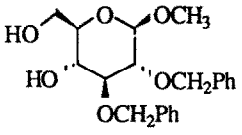
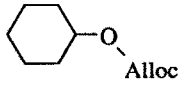
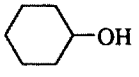
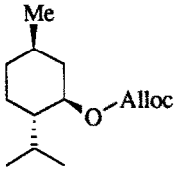
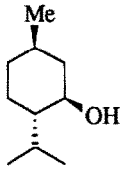
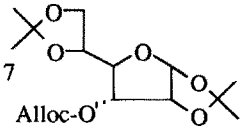
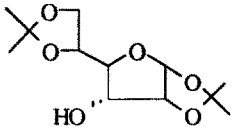
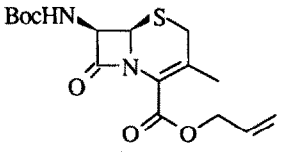
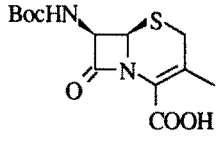
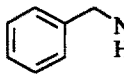
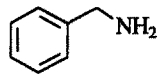
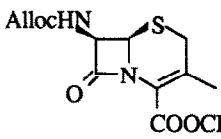
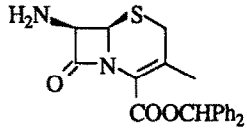
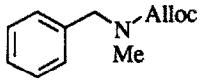
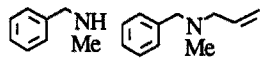
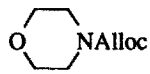
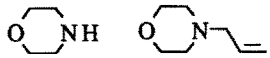
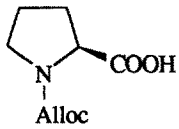
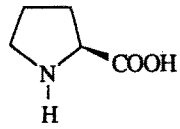
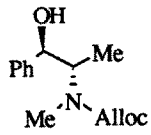
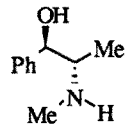
entry	substrates	NuH (eq)	product	Pd(0) (mol%)	solvent	time /r.t.	yield %
1		Et_2NH 5		2	CH_3CN/H_2O	5min	94
2	"" ""	HCOOH 3.5	"" ""	2	CH_3CN/H_2O	2.5h	51
3	"" ""	Et_2NH 5	"" ""	2	CH_2Cl_2/H_2O	3min	76
4		2.2		2	CH_3CN/H_2O	20min	99
5		2.2		2	CH_3CN/H_2O	10min	80
6		2.2		2.2	C_3H_7CN/H_2O	30min	100
7		2.2		2	CH_3CN/H_2O	10min	99
8		10		2	$CH_3CN/MeOH/H_2O$	1h	93

Table II : Palladium Mediated Deprotection of Amines with $Pd(OAc)_2$ / TPPTS, Et_2NH.

entry	substrates	$HNEt_2$ (eq)	product	Pd(0) (mol%)	solvent	time / r.t.	yield %
1		2.2		0.5	CH_3CN/H_2O	10min	100
2	" "	5	" "	1	C_3H_7CN/H_2O	15min	100
3	Alloc-NH-NH-Alloc	2.2	NH_2-NH_2	2	CH_3CN/H_2O	5min	99
4		2.2		2	$CH_3CN/MeOH/H_2O$	6h	73
5		2	 30% 70%	2	CH_3CN/H_2O	5min	100
6	" "	40	97% 3%	2	CH_3CN/H_2O	5min	100
7	" "	8	90% 10%	2	Et_2O/H_2O	5min	100
8	" "	5	100% 0%	5	C_3H_7CN/H_2O	15min	100
9		5	 98% 2%	2.5	C_3H_7CN/H_2O	10min	100
10		2.2		2	CH_3CN/H_2O	15min	100
11		5		2	CH_3CN/H_2O	15min	100

The deprotection of secondary amines is difficult using this procedure. Indeed the same conditions Pd-TPPTS / $HNEt_2$ (2.eq.) used with alloc-carbamate of N,N benzylmethylamine afford substantial amount of the undesired allylamine (entry 5). However with a 40 fold excess of this volatile allyl scavenger, the benzylmethylamine was recovered in 97% with a trace (3%) of the undesired N-allylmethylbenzylamine (entry 6). When deprotection was conducted under biphasic conditions (ether / water) and using only 8 fold excess of diethylamine a substantial decrease of the N allylated amine (10%) is seen (entry 7). This undesired product is totally suppressed in the presence of diethylamine (5 fold excess) in butyronitrile / water system (entry 8). N-allyloxycarbamates derived from secondary amines (e.g. morpholine, proline, ephedrine) reacted equally well on treatment with $HNEt_2$ (2.2-5 fold excess) in the presence of $Pd(OAc)_2$-TPPTS catalytic system at room temperature within 10-15 min.. The parent molecules were recoverd in quantitative yield as shown in table II (entries 9, 10, 11).

Conclusion

Our present unexpensive procedure to deprotect the alloc group of alcohols, primary and secondary amines using the palladium catalyzed reaction under aqueous conditions enhances the value of alloc as protecting group in organic synthesis. This technology allows easy separation of the free alcohols, amines, acids in almost pure form from the catalyst. In addition the water soluble catalyst is easily recycled. The method is simple and particularly efficient and synthetic applications to fine organic syntheses are underway in our laboratory. This new procedure demonstrates significant advantages to existing procedures.

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Experimental section

Starting materials and products were charaterized by IR, ^1H, and ^{13}C NMR and MS .
^1H and ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker AM-200 or Brucker AM-250 Fourier transform spectrometer. Spectra were obtained in chloroform-d. Infrared (IR) spectra were recorded on a Brucker 45. Mass Spectra were obtained on a Helwett-Packard 5890-II gas chromatograph using SE 30 column (12m, 0.2 ϕ int., 0.33μm) with an HP 5989-A mass detector (70 eV). Flash chromatography was performed using 0.040-0.063mm silica gel (E. Merck, Si 60). The reaction mixtures were analyzed by G.C. (Helwett Packard 5890-II apparatus) with a SE 30 column and helium as carrier gas. The main parameters are : initial temperature 60°C; final temperature 160°C; rate : 10°C/min; injector and detector temperatures 220°C.
All starting allyloxycarbonates or carbamates were prepared under the usual conditions.[12] The following experimental procedures are representative :

A- Amine protection

N-allyloxycarbonyl-N-methylbenzylamine.
To a solution of N-methylbenzylamine (4.26 g, 35.2 mmol.) in CH_2Cl_2 (40 mL) was added allylchloroformiate (0.5 eq.) at 0°C. After stirring 15 min , the reaction mixture was allowed to room temperature. A white solid precipitated and after 1h the solution was filtered and solvent was removed at reduced pressure. The residue was treated by water and the mixture was extracted by $CHCl_3$. The extracts were combined, washed, dried filtered on short silica gel column and concentrated under vacuo.
m = 3.3g (97.5%) of a translucent oil.

diphenylmethyl (6R)(7R)-3-methyl-7-(N-Alloc-amino)-8-oxo-3-cephem-4-carboxylate.
A suspension of diphenylmethyl (6R)(7R)-3-methyl-7-(amino)-8-oxo-3-cephem-4-carboxylate (0.26g, 0.684 mmol) in AcOEt (10 mL) was cooled to 0°C and triethylamine (1.1 eq.) then allylchloroformiate (3 eq.) were added dropwise. The reaction mixture wad allowed to room temperature and after 3h., the solution was filtered and solvent was removed at reduced pressure.The residue was treated by water and the mixture was extracted by AcOEt.The extracts were combined, washed, dried, and concentrated under vacuo to give 0.22 g (88%) of a solid.

B- Alcohol protection.

Alloc-menthol.
To a solution of (1R)(2S)(5R) menthol (3 g, 1.92 mmole) in THF (30 mL) were added allylchloroformiate (6.12 mL, 3 eq.) and pyridine (4.63 mL, 3 eq.) at 0°C. After stirring 15 min, the reaction mixture was allowed to room temperature. A white solid precipitated and after 12h the solution was filtered and solvent was removed at reduced pressure. The residue was treated with water and the mixture was extracted with Et_2O. The extracts were combined, washed, dried filtered on a short silica gel column and concentrated under vacuo to give 4.62g (100.%) of a translucent oil.

6-O-Allyloxycarbonyl methyl-2,3-di-O-benzyl-α-L-glucopyranoside.

To a solution of methyl-2,3-di-O-benzyl-α-L-glucopyranoside (0.5 g, 1.337 mmol.) in THF (10 mL) were added allylchloroformiate (0.17 mL, 1.2 eq.) and pyridine (0.33 mL, 3 eq.) at 0°C. After stirring 15 min , the reaction mixture was allowed to room temperature. A white solid precipitated and after 3h the solution was filtered and solvent was removed at reduced pressure. The residue was treated with water and the mixture was extracted with AcOEt. The extracts were combined, washed, dried filtered on short silica gel column and concentrated under vacuo to give 0.61g (99.6%) of a translucent oil.

Deprotection of 4-(diphenylmethyl) (6R) (7R)-3-methyl-7-(N-Alloc-amino)-8-oxo-3-cephem-4-carboxylate.
A solution of the carbamate (0.1g, 0.216 mmol) in the presence of $Pd(OAc)_2$ (0.96 10^{-3} g, 2%), TPPTS (4.78 10^{-3} g, 4%) and diethylamine (0.049 mL, 2.2 eq.) in acetonitrile/water/methanol was stirred 6h. at 20°C. After completion, the crude product was filtered on silicagel and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to give 0.06 g (73%) of a solid.

Deprotection of Alloc-morpholine.
A solution of Alloc-morpholine (0.25g, 1.46 mmol) in the presence of $Pd(OAc)_2$ (8.2 10^{-3} g, 2.5%), TPPTS (41 10^{-3} g, 5%) and diethylamine (0.754 mL, 5 eq.) in butyronitrile/water was stirred 10 min. at 20°C. After completion, the crude product was filtered on silicagel and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to give 0.127 g (100%) of a translucent oil.

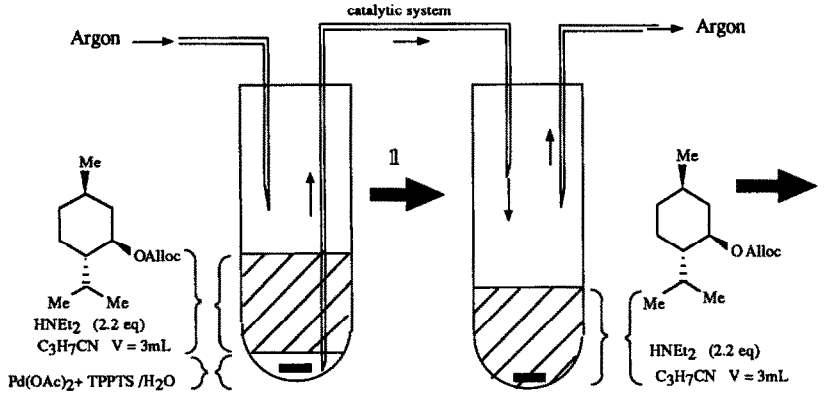
Deprotection of Alloc-L-proline.
A solution of Alloc-L-proline (0.25g, 1.25 mmol) in the presence of $Pd(OAc)_2$ (5.6 10^{-3} g, 2%), TPPTS (28 10^{-3} g, 4%) and diethylamine (0.284 mL, 5 eq.) in butyronitrile/water was stirred 15 min. at 20°C. After completion, the crude product was filtered on silicagel and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to give 0.144 g (100%) of a solid.

Deprotection of 6-O-Allyloxycarbonyl methyl-2,3-di-O-benzyl-α-D-glucopyranoside.
A solution of the carbonate (0.2g, 0.422 mmol) in the presence of $Pd(OAc)_2$ (2 10^{-3} g, 2%), TPPTS (9.4 10^{-3} g, 4%) and diethylamine (0.096 mL, 2.2 eq.) in acetonitrile/water was stirred 20 min. at 20°C. After completion, the crude product was filtered on silicagel and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to give 0.156 g (99%) of a solid.

Deprotection of Alloc-menthol and recycling of the catalyst.
A solution of the carbonate (0.2 g, 0.83mmol), in the presence of $Pd(OAc)_2$ (2%), TPPTS (4%) and diethylamine (2.2 eq.) in butyronitrile/water was stirred 30 min. at 20°C. After completion, the crude product was filtered on silicagel and after evaporation of the solvent in vacuo, was purified by flash chromatography to give 0.13 g of a white solid. The catalytic system can be recycled (10 times) as presented on the scheme below without loss of activity. The apparatus was flushed by an argon flow. The two flasks

are linked by a siphon tube. The catalyst solution (lower phase) was transferred under argon pressure in the second flask containing a fresh solution of Alloc-menthol.

Thus 2.2 g (9.16 mmol) of Alloc- menthol were deprotected using 9.32 10^{-3} g (0.041 mmol, 5%) of $Pd(OAc)_2$, 4.6 10^{-2} g (0.083 mmol, 10%) of TPPTS and 2 mL of Et_2NH 1.43 g (9.16 mmol) of (-)-menthol were recovered.



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