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PALLADIUM-CATALYZED REACTION OF TRIBUTYLTIN HYDRIDE. SELECTIVE AND VERY MILD DEPROTECTION OF ALLYL AND ALLYLOXYCARBONYL DERIVATIVES OF AMINO-ACIDS.

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Summary :

Allyl(All) and Allyloxycarbonyl(Alloc) amino-acid derivatives are deprotected through palladium-catalyzed hydrostannolysis by Bu_3SnH in a highly selective manner. Benzyl and benzyloxycarbonyl groups are stable under these conditions. Moreover the allyl and Alloc groups seem orthogonal to the t-butyl and t-butoxycarbonyl protecting groups.

The allyloxycarbonyl group first introduced by Stevens and Watanabe[1] has been proposed on several occasions for the protection of amines and alcohols. Early deprotection procedures include reductive cleavage[1] or $Ni(CO)_4$ promoted cleavage[2] of the allylic group. In addition, carboxylic acids protected as their allyl esters have been unblocked by means of organocuprate reagents[3].

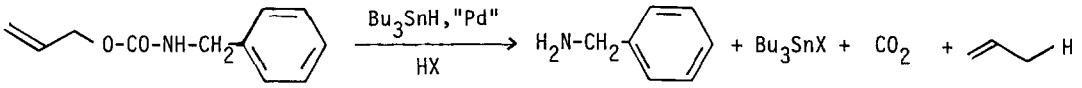
With the development of palladium π-allyl chemistry, new methods based on homogeneous palladium catalysis has been devised for the cleavage of allylic phenoxides, carboxylates, carbonates and carbamates. These methods include the transfer of the allyl group to dimedone[4], or the 2-ethylhexanoic acid or its potassium salt[5] as well as several hydrogenolytic cleavages using formic acid[6], ammonium formates[7] or sodium borohydride[8] as the reducing agent[9].

We have earlier proposed[10] a very mild and selective deprotection method of allyl carbonates based on a palladium-catalyzed hydrostannolytic cleavage with tributyltin hydride. Deprotection of allyl carbamates and allyl phenyl ethers under similar conditions was also briefly reported[11]. With the ultimate goal of applying this methodology to peptide synthesis we report here a more detailed study of these reactions, mostly performed on amino-acids and amino-acids derivatives.

The palladium-complex used in this work was the readily prepared[12], air-stable palladium(II) dichlorobistriphenylphosphine. The true catalytic species, however, is in all probability the coordinatively unsaturated palladium(0) bistriphenylphosphine which forms instantaneously in

situ upon reduction by tributyltin hydride.

In a first set of experiments, we investigated the range of solvents compatible with the catalytic hydrostannolytic procedure. Allyloxycarbonylbenzylamine was used as the model substrate. In the presence of a proton donor such as acetic acid or p-nitrophenol, quantitative and quasi-instantaneous deprotection was observed at room temperature in benzene, toluene, diethyl ether, THF, dichloromethane, ethylacetate, acetone and DMF. In moist dichloromethane, deprotection could also be carried out in the absence of other acidic species[13].



"Pd" = $PdCl_2(PPh_3)_2$,2%
HX = pNO_2PhOH, CH_3CO_2H, $CH_3CO_2^-PyH^+$

The results on the deprotection of various representative amino-acid derivatives[14] are presented in the Table. The reactions were run mostly in moist dichloromethane and without acidic additive. A slight excess (1.3 eq) of tributyltin hydride was ordinarily used for the hydrostannolytic cleavage ; however the exact amount of reducing agent is not an important factor for these reactions since any tributyltin hydride in excess is rapidly decomposed, under palladium catalysis, into the chemically inert hexabutyldistannane[11,16]. Hexabutyldistannane as well as other tributyltin by-products of the reactions are highly or freely soluble in non-polar solvents (hydrocarbons, diethyl ether) and thus easy to eliminate.

Hydrostannolytic cleavage of carboxy-free N-α-allyloxycarbonyl amino-acid derivatives (entries 1-6,10) in moist dichloromethane resulted in immediate precipitation of the free amino-acid. With carboxyprotected N-allyloxycarbonyl derivatives (entries 7-9) the corresponding tributyltin carbamate intermediate (υ (CO) 1640 cm^{-1}, $CHCl_3$) was obtained[15]. Conversion to the free amino-acid was immediate upon treatment with acetic acid, acetic acid/pyridine or p-nitrophenol. Allyl esters (entry 9) were converted to tributyltin carboxylates (υ (CO) 1650 cm^{-1}, $CHCl_3$) which upon protonolysis (one equivalent TsOH or aqueous HCl) liberated the free carboxylics acids.

The presents results deserve several comments : first, the catalytic hydrostannolytic process is not affected by the presence of the methylthio group of methionine (entry 2). Secondly, it is specific for the allyloxycarbonyl group and for the allyl group (allyl carboxylate -entry 8- or allyl ether of tyrosine -entry 6-).

The benzyl (Bzl) and benzyloxycarbonyl (Z) groups as well as the terbutyl and terbutoxycarbonyl (BOC) groups are perfectly stable under these conditions (see entry 9 and the cross-experiments of entries 7-8 and 10-11). Moreover the allyloxycarbonyl and allyl group on one hand and the terbutyl and terbutoxycarbonyl group on the other appear to be orthogonal, as we were able to remove the latter from N-alloc-Ser(OtBu)terbutylester, Nα-Alloc Nε-BOC lysine

and Nα-BOC Nε-Alloc-lysine under standard conditions (CH_2Cl_2/CF_3CO_2H, 1/1, 3 hrs, room temperature, without affecting the N-allyloxycarbonyl protection (see also ref. 4). Thirdly, in spite of the fact that palladium complexes are known to catalyze the decarboxylative conversion of allyl carbamates to allyl amines[7a], due probably to the quasi-instantaneous character of the hydrostannolytic process, no allyl amines could be detected in our reactions. Such is not always the case in the corresponding catalytic hydrogenolytic cleavage with formic acid

TABLE

Entry	Protected amino-acid	Deprotected product	Yield[b]
1	Alloc-Gly-OH	Gly	>95 %
2	Alloc-Met-OH	Met	>95 %
3	Alloc-Leu-OH	Leu	>95 %
4	Alloc-Phe-OH	Phe	>95 %
5	Alloc-Tyr(-OAlloc)-OH	Tyr	>95 %
6	Alloc-Tyr(OAll)-OH	Tyr	>95 %
7	Alloc-Phe-OBzl	H-Phe-OBzl[c]	90 %
8	Z-Phe-OAll	Z-Phe-OH	90 %[d]
9	Alloc-Ser(OtBu)-OtBu	H-Ser(OtBu)-OtBu[e]	70 %
10	Alloc-Lys(BOC)-OH	H-Lys(BOC)-OH	85 %
11	BOC-Lys(Alloc)-OH	BOC-Lys-OH	95 %[f]

(a) L series ; Alloc : -C(O)O~, All : ~ ; Z -C(O)OCH_2Ph ; BOC : -C(O)OtBu.
(b) Isolated yield unless otherwise noted. Crude reaction mixtures were always found by NMR, IR and ccm standard, free from starting material and from amino-acid compounds other than the expected one.
(c) Isolated as its p-toluenesulfonate salt.
(d) Analytical yield (NMR anisole as the reference) after extraction of the crude reaction mixture with aqueous HCl to eliminate all possible free amino compounds.
(e) F.M. Callanan, G.W. Anderson, R. Paul and J.E. Zimmerman, J. Am. Chem. Soc., 85, 202 (1963).
(f) Analytical yield (NMR) on the crude reaction mixture.

derivatives[7a,b]. Finally, the hydrostannolytic cleavage of the allyloxycarbonyl group does not induce any racemization at the chirality centers. This was thouroughly checked in the case of Alloc-L methionine by gas chromatography analysis on a chiral column of the deprotected amino-acid after appropriate derivatization[17]. Likewise, the dipeptide BOC-L Leu-L Met-NH_2 1 obtained via the sequence :

$$\text{Alloc-L Met} \xrightarrow[2)\ NH_3/H_2O]{1)\ iBuOCOCl/Et_3N} \text{Alloc-L Met-}NH_2 \xrightarrow[2)\ \text{BOC-L Leu-OSu}]{1)\ Bu_3SnH/Pd} \quad 1$$

was found to be diastereoisomerically pure (HPLC, comparison with authentic samples).

All these features coupled with a great tolerance with respect to the nature of the solvent used strongly recommend the allyl and allyloxycarbonyl protecting group and their deprotection via catalytic hydrostannolysis in peptide synthesis. We are currently investigating this field, especially in solid phase peptide synthesis[18].

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13- For unclear reasons, deprotection is not complete in other solvents in the absence of a proton donor. The remaining allyloxycarbonyl derivative is then slowly converted to allyl and diallyl benzylamine (see ref. 7a).
14- N-allyloxycarbonyl[1] and N-benzyloxycarbonyl derivatives were synthetized by known procedures. Z-Phe-O-All and Alloc-Phe-OBzl were prepared by esterification (F. Matsuda, S. Itoh, N. Hatori, M. Yanagiya and T. Matsumoto, Tetrahedron, 41, 3625 (1985) of the corresponding N-protected amino-acid. Alloc-Ser(OtBu)OtBu was obtained from Alloc-Ser-OH by the procedure of E. Schroder (Chem. Ber., 670, 127 (1963). All compounds were recrystallized or purified by column chromatography or by recrystallization of their dicyclohexylammonium salts in the case of carboxyl free derivatives. They were thorougly identified by infra-red and NMR spectroscopy. Typical examples : Alloc-Tyr(OAlloc)-OH : IR($CDCl_3$) 1750, 1710(br) cm^{-1} ; ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) : 8.35 (s), 7.22-7.1 (m, 4H), 6.06-5.85 (m, 2H, vinyl CH), 5.35-5.15 (m, 4+1)H, NH, vinyl CH_2), 4,7 (d, J = 8 Hz 2H, CH_2 OCOO), 4.65 (t, J ≅ 8 Hz, 1H, αCH), 4.5 (br.d) J ≅ 8 Hz, 2H, CH_2O-CONH), 3.1 (ABX, J_{AB} = 15 Hz, J_{AX} = J_{BX} = 8 Hz, CH_2-Ph).
Alloc-Tyr (OAll)-OH : IR ($CHCl_3$) : 1710 (br) cm^{-1} : ^1H NMR ($CDCl_3$) : 6.8-7.4 (m, (4+1)H), 6.1-5.6 (m, 2H, vinyl CH), 5.55-5.0 (m, (4+1)H, NH, vinyl CH_2), 4.8-4.4 (m, 5H, allylic H, αCH), 3.2-2.9 (m, 2H, CH_2Ph).
15- N-tributyltinoxycarbonyl phenylalanine benzyl esters was purified by column chromatography (silicagel, cyclohexane/Et_2O 80/20) 60 % yield.
IR (CCl_4) 1740, 1640 cm^{-1} ; ^1H NMR ($CDCl_3$, 250 MHz) : 7.4-7.1 (m, 10 H), 5.1 (s, 2H, OCH_2 Ph), 3.75 (t, J = 8 Hz, 1H), 3.0 (ABX, J_{AB} = 15 Hz, J_{AX} = J_{BX} = 7 Hz, 2H ; 2.6-0.9 (m, 27H, Bu_3Sn).
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18- As a first result, the tripeptide Gly-Leu-Met NH_2 was obtained in 66 % using a Methylbenzhydrylamine resin and final cleavage with hydrogen fluoride (work in collaboration with S. Lavielle, G. Chassaing and A. Marquet, Laboratoire de Chimie Organique Biologique, Université de Paris VI).

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