Hexadienyloxycarbonyl (Hdoc) – A Mild Acid Labile Protecting Group for Amines

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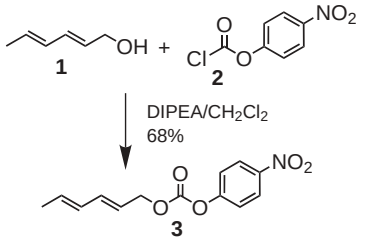
Abstract: Hexadienyloxycarbonyl is an amine protecting group which can be cleaved with 1% TFA in CH_2Cl_2. It is stable to Pd(0) and basic conditions and is proposed as a useful alternative to the trityl and Bpoc protecting groups.

Key words: protecting groups, amines, amino acids, cleavage, protonations

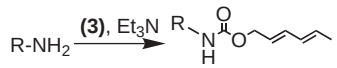
Protecting groups are essential tools for the synthetic chemist in the construction of complex organic molecules. The usefulness of any protecting group relies on its ease of synthesis and introduction, its stability to a range of reaction conditions, and the selectivity, efficiency and relative 'orthogonality' of its cleavage with respect to other protecting groups.[2] Here we report the synthesis, introduction and cleavage of a protecting group, observed to be 'orthogonal' to a wide variety of existing protecting groups, yet readily cleaved under mildly acidic conditions.

The protecting group was readily incorporated using *E,E*-2,4-hexadienyl-(4-nitrophenyl) carbonate (**3**)[3] which was readily prepared by the reaction of *E,E*-hexadien-1-ol (**1**) with *p*-nitrophenylchloroformate (**2**) in the presence of DIPEA (Scheme 1). This activated carbonate could be stored at –20 °C for three months without degradation.



Scheme 1 Synthesis of the activated reagent for Hdoc protecting group introduction.

Amino protection of a variety of amines [aniline (**4**), benzylamine (**5**), 3-phenylpropylamine (**6**) and phenylalanine (**7**)] with the Hdoc moiety was easily achieved by reaction with 1 equivalent of compound **3** in the presence of triethylamine (Scheme 2).



4 R=Ph
5 R=CH_2Ph
6 R=$CH_2CH_2CH_2$Ph
7 R=CH(CH_2Ph)CO_2H

8 R=Ph 81%
9 R=CH_2Ph 96%
10 R=$CH_2CH_2CH_2$Ph 94%
11 R=CH(CH_2Ph)CO_2H 69%

Scheme 2 Hdoc protection of amines (**4**–**8**)

It was found that the Hdoc group could be readily cleaved from the amino acid under a variety of acidic conditions (Table 1, entries 1–6), returning phenylalanine. The moiety was found to be stable to all of the other conditions investigated, but RP-HPLC analysis showed that reaction with iodine caused modification to the molecule (entry 12) and treatment of this modified compound with 10% TFA in CH_2Cl_2 failed to cleave the protecting group.

The mild acid cleavage of the group can be explained by resonance stabilisation of the cation across the conjugated diene system and the generation of carbon dioxide (cf. to the Boc group). Proton abstraction from any of the resonance structures would lead to the formation of 1,3,5-hexatriene as the by product, however GC-MS analysis of the cleavage products suggested that the cation was quenched by reaction with TFA yielding a mixture of hexadienyltrifluoroacetates, although it was not possible to confirm the identity of these by-products by NMR.

The non-cleavage modification of Hdoc-Phe-OH by palladium(0) was somewhat unexpected due to the similarity with the Aloc group, which is selectively cleaved by treatment with palladium(0). One could surmise that the Hdoc group would be cleaved in a similar manner, or modified by complexation of the palladium by the diene moiety. In order to confirm that this was not the case, the treatment of Hdoc-Phe-OH with palladium(0) was repeated on a larger scale and the product isolated. HPLC-MS and NMR confirmed the recovery of unmodified Hdoc-Phe OH in 87% yield following purification and work-up, suggesting that it is essentially stable to these conditions.

In summary, the hexadienyloxycarbonyl or Hdoc group is a new mild acid cleavable protecting group for amines. It is stable to a wide variety of conditions, including many that are used for the removal of other protecting groups. The group may be a useful alternative to the trityl group where the latter's steric bulk may cause synthetic difficulties or provide a more acid labile variant of the widely used Boc group.

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Table 1 Stability of the Hdoc Group to a Variety of Conditions

	Cleavage conditions	TLC				HPLC	Conclusion
		10 min	1 h	2 h	16 h	16 h	
1	95% TFA/CH_2Cl_2[4]	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved
2	10% TFA/CH_2Cl_2[5]	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved
3	1% TFA/CH_2Cl_2[6]	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved	Cleaved
4	0.1% TFA/CH_2Cl_2	Stable	Stable	Partially cleaved	Partially cleaved	Partially cleaved	Slowly cleaved
5	4 M HCl/dioxane	Stable	Partially cleaved	Partially cleaved	Partially cleaved	Cleaved	Slowly cleaved
6	2 M HCl/H_2O	Stable	Stable	Stable	Cleaved	Mainly cleaved	Slowly cleaved
7	10% AcOH/CH_2Cl_2	Stable	Stable	Stable	Stable	Stable	Stable
8	20% pip/DMF[7]	Stable	Stable	Stable	Stable	Stable	Stable
9	5% DBU/CH_2Cl_2	Stable	Stable	Stable	Stable	Stable	Stable
10	$Pd(PPh_3)_4$ in $CHCl_3$/ AcOH/NMM (37:2:1)[8]	Stable	Stable	Stable	Stable	Stable	Stable
11	2 M NaOH/H_2O	Stable	Stable	Stable	Stable	Stable	Stable
12	1 M I_2 in DMF	Modified	Modified	Modified	Modified	Modified	Modified
13	5% H_4N_2/DMF[9]	Stable	Stable	Stable	Stable	Stable	Stable
14	100 °C/DMF	Stable	Stable	Stable	Stable	Stable	Stable
15	1 M $NaBH_4$ in THF	Stable	Stable	Stable	Stable	Stable	Stable
16	UV light/CH_2Cl_2	Stable	Stable	Stable	Stable	Stable	Stable
17	1 M TBAF in THF[10]	Stable	Stable	Stable	Stable	Stable	Stable

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(3) 2,4-*E*,*E*-Hexadien-1-ol (10 g, 98 mmol) was dissolved in CH_2Cl_2 (50 mL) and *p*-nitrophenylchloroformate (21 g, 105 mmol) was added. DIPEA (18.3 mL, 105 mmol) was added dropwise with cooling, and the solution was stirred for 16 hours at room temperature under N_2. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel eluting with 5% EtOAc in hexane. The product was recrystallised from hexane/EtOAc to give a white solid. (17.4 g, 68%); δ_H (400 MHz, $CDCl_3$), 1.70–1.72 (d, *J* = 7 Hz, 3 H, C*H*$_3$), 4.69–4.71 (d, *J* = 7 Hz, 2 H, CHC*H*$_2$O), 5.58–5.65 (dq, *J* = 7 Hz, 12 Hz, 1 H, CH_3C*H*CH), 5.71–5.80 (dt, *J* = 7 Hz, 15 Hz, 1 H, CHC*H*CH$_2$), 5.98–6.05 (dd, *J* = 10 Hz, 12 Hz, 1 H, CH_3CHC*H*), 6.25–6.32 (dd, *J* = 10 Hz, 15 Hz, 1 H, C*H*CHCH$_2$), 7.29–7.32 (d, *J* = 9 Hz, 2 H, *o*-Ar*H*), 8.19–8.21 (d, *J* = 9 Hz, 2 H, *m*-Ar*H*); δ_C (101 MHz, $CDCl_3$), 18.6 (*C*H$_3$), 70.2 (*C*H$_2$), 122.0 (CH_3*C*H), 122.2 (*o*-Ar*C*), 125.7 (*m*-Ar*C*), 130.5 (CH_3CH*C*H), 133.2 (*C*HCH$_2$), 137.4 (*C*HCHCH$_2$), 145.8 (*p*-Ar*C*), 152.8 (*C*=O), 156.0 (*i*-Ar*C*).
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