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THE CINNAMYLOXYCARBONYL GROUP AS A NEW AMINO-PROTECTING GROUP

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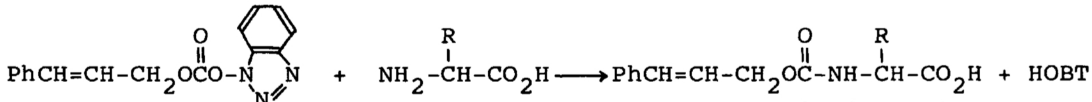
A new urethane-type protecting group for amines, cinnamyloxycarbonyl (Coc) group, is described. The cleavage of the Coc group is effectively catalyzed by 5 mol% of $[Pd(PPh_3)_4]$ in the presence of formic acid, pyridine, and N-hydroxysuccinimide in refluxing THF. The Z- and Boc-protecting groups are not affected under the same reaction conditions.

A variety of amino-protecting groups have been developed and especially urethane-type protecting groups such as the benzyloxycarbonyl (Z) and the t-butoxycarbonyl (Boc) groups have been widely employed in peptide syntheses.[1)]

In connection with our recent investigation on the palladium catalyzed reaction of allylic acetates and sulfones, we have planned to develop a new amino-protecting group which can be removed selectively under mild conditions in the presence of Z- and Boc-protecting groups. Herein we report a new urethane-type group, cinnamyloxycarbonyl (Coc) group which can be easily introduced to amino acids and efficiently removed with the aid of a catalytic amount of $[Pd(PPh_3)_4]$. The Coc-protected amino acid esters or dipeptide esters were also selectively deprotected in the presence of Z- and Boc-protected amino acid N-hydroxysuccinimide esters giving the corresponding peptides in one pot in good yields.

Introduction of Coc group to amino acids was performed by the reaction of a crystalline reagent, 1-(cinnamyloxycarbonyl)benzotriazole (Coc-OBT, 1),[2)] and various amino acids in good yields. The following procedure is representative for the preparation of Coc-amino acids: To a suspension of H-Ala-OH (89 mg, 1 mmol) in water (1 ml) was added a solution of 1.5 equiv. of triethylamine (TEA) (155 mg, 1.5 mmol) in DMF (1 ml) followed by the addition of a solid of 1 (325 mg, 1.1 mmol). The reaction mixture was allowed to stand overnight at room temperature, diluted with 5 ml of water, and then extracted with AcOEt twice and the aqueous layer was acidified by 6 M HCl. The liberated oil was extracted with ether twice and the combined extracts were washed with 6 M HCl and brine, and dried over $MgSO_4$. Removal of the ether gave Coc-Ala-OH (2a) in 95% yield (236 mg, mp 74.5-75.0 °C).



1 2a (R=CH_3)

In a similar manner, a variety of Coc-amino acids (2b-n) were prepared in good yields as shown in Table 1.

Recently, Tsuji and Yamakawa have reported that allylic esters were effectively reduced with HCO_2NH_4 and a catalytic amount of palladium complex.[3] Therefore, Coc-Gly-OEt derived from 1 and H-Gly-OEt was treated with 5 mol% of $[Pd(PPh_3)_4]$, formic acid, and pyridine (Py), however, the satisfactory result was not obtained. From the fact that the N-cinnamylated product was observed as a by-product, it seemed to be necessary to scavenge cinnamyl cation, which exists as π-allyl complex of palladium in the reaction, completely. Ultimately, the addition of N-hydroxysuccinimide (HONSu) was so effective that the above N-cinnamylation reaction could be suppressed almost completely. Furthermore, the treatment of Coc-Gly-OEt under the same conditions in the presence of Z-Gly-OSu gave the desired Z-Gly-Gly-OEt (3a) in good yield. Namely, to a solution of Z-Gly-OSu (61 mg, 0.2 mmol), Coc-Gly-OEt (53 mg, 0.2 mmol), and HONSu (23 mg, 0.2 mmol) in dry THF (4 ml) was added a solution of HCO_2H (19 mg, 0.4 mmol) and Py (63 mg, 0.8 mmol) in dry THF (1 ml) under N_2. Then, a solution of $[Pd(PPh_3)_4]$ (12 mg, 0.01 mmol) in dry THF (1 ml) was added to it. The mixture was refluxed for 4 min, cooled, and allowed to stand overnight at room temperature. After quenching the reaction with aq KCN, the solvent was removed in vacuo to give a residue which was taken up into AcOEt. The AcOEt solution was washed successively with water, 1 M HCl, 10% $NaHCO_3$, and brine, and dried over $MgSO_4$. Removal of the solvent gave a crude product which was purified by a preparative TLC (solvent; hexane:AcOEt=1:3 v/v) to afford 3a in 92% yield (54 mg).[4]

In a similar way, various N-protected di- and tripeptide esters (3b-f) were

Table 1. Preparation of Coc-Amino Acids (2a-n)

$$\text{H-A.A.-OH}^{a)} + \underline{1} + \text{TEA} \xrightarrow[\text{r.t., overnight}]{\text{H}_2\text{O-solvent}} \text{Coc-A.A.-OH} \;\; \underline{2a\text{-}n}$$

Coc-A.A.-OH[b)]		Solvent	Yield/%	Mp θm/°C	$[\alpha]_D^{27}$ /°(c, solvent)	
2a	Ala	DMF	95	74.5-75.0	-8.4	(2.00, absEtOH)
2b	β-Ala	dioxane	87	97-98		
2c	Asp	dioxane	83	135	+1.5	(3.95, absEtOH)
2d	Gln	DMF	91	119-122	-9.3	(1.07, MeOH)
2e	Gly	dioxane	83	129.5-130.5		
2f	His(Bzl)	dioxane	83	217-218	+11.5	(1.05, DMF)
2g	Leu	DMF	93	143-144[c)]	-3.6	(1.10, DMF)
2h	Ile	dioxane	94	127-128[c)]	+10.8	(1.02, MeOH)
2i	Met	DMF	93	82.5	-14.9	(1.00, absEtOH)
2j	Phe	dioxane	73	97.0-98.0	+5.1	(2.00, absEtOH)
2k	Pro	dioxane	71	119-121[c)]	-16.2	(1.06, DMF)
2l	Ser	dioxane	81	95-97	+12.0	(1.08, MeOH)
2m	Thr	dioxane	71	101.0-102.0	+2.6	(3.51, absEtOH)
2n	Val	dioxane	quant	101	+3.0	(1.66, absEtOH)

a) H-A.A.-OH means an amino acid.
b) All elemental analyses exhibited satisfactory values in accordance with assigned structure.
c) Characterized as dicyclohexylammonium salt.

Table 2. Preparation of Z-and Boc-Peptide Esters (3a-f)

$$\begin{matrix}\text{Coc-A.A.-OR or}\\ \text{Coc-dipeptide-OR}\end{matrix} \xrightarrow[\text{HCO}_2\text{H, reflux, 4 min, in THF}]{\text{Py, HONSu, [Pd(PPh}_3)_4]} \begin{bmatrix}\text{H-A.A.-OR or}\\ \text{H-dipeptide-OR}\end{bmatrix} \xrightarrow{\text{Y-A.A.-OSu}^{a)}} \underline{3a\text{-}f}$$

Coc-derivative	Product	Yield/%	Mp θm/°C	$[\alpha]_D^{23}$ /°(c, Solvent)
Coc-Gly-OEt	Z-Gly-Gly-OEt (3a)	92[c)]	81-82[5)]	
Coc-Gly-OEt	Z-Ala-Gly-OEt (3b)	75	99-100	-22.3 (2.10, EtOH)[6)]
Coc-Gly-OEt	Boc-Leu-Gly-OEt (3c)	87	83-84	-30.5 (1.05, MeOH)[7)]
Coc-Met-OMe	Boc-Phe-Met-OMe (3d)	79	84-84.5	-25.5 (0.51, MeOH)
Coc-Leu-Gly-OEt[b)]	Boc-Pro-Leu-Gly-OEt (3e)	91	103-105	-59.9 (1.00, DMF)[8)]
Coc-Gly-Gly-OEt[b)]	Z-Gly-Gly-Gly-OEt (3f)	70	164[9)]	

a) Y means Boc or Z groups.
b) They were prepared by the reaction of 2e or 2g with H-Gly-OEt using BID-OSu[10)] as a condensing reagent.
c) Yield was 80% in the absence of formic acid.

prepared in high yields as summarized in Table 2.

As mentioned above, advantages of the Coc-protecting group are as follows: 1) it can be readily introduced to an amino acid using the stable crystalline reagent 1; 2) the conditions for deprotection are extremely mild and specific for it and are compatible with Z- and Boc-protecting groups; 3) it is also removable in the case of methionine derivative containing sulfur; 4) it can be monitored on a TLC plate containing a fluorescent indicator (254 nm).

Further studies on the scope and limitation of the Coc-protecting group in peptide synthesis are now undergoing.

References

1) E. Gross and J. Meienhofer, " The Peptides," Academic Press, New York(1981), Vol.3.
2) Coc-OBT was prepared in a way similar to the reported ones.[11] To a solution of phosgene (9.8 g, 0.1 mol) in dry ether (30 ml) was added a solution of cinnamyl alcohol (13.4 g, 0.1 mol) in dry ether (40 ml) at -40 °C. The solution was gradually warmed and allowed to stand overnight at room temperature. The solvent was removed in vacuo at 0 °C to give a brownish oil which was taken up into dry CH_3CN (80 ml) immediately. To the vigorously stirred solution were added a solid of 1-hydroxybenzotriazole monohydrate(HOBT) (15.3 g, 0.1 mol) and then a solution of TEA (11.1 g, 0.1 mol) in dry CH_3CN (30 ml) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and poured into 800 ml of water. A crystalline compound was collected, washed with a small amount of water, and dried (21.6 g, 73%). Recrystallization from benzene gave pure Coc-OBT in 70% yield (20.6 g,), mp 125 °C (dec). Found: C, 65.20; H, 4.34; N, 14.26%. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23%. Coc-OBT obtained thus is quite stable on storage at room temperature.
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4) H. Kunz and C. Unverzagt have used dimedone as a scavenger of allyl cation: Angew. Chem., 23, 436 (1984). Then, the coupling reaction was carried out under the same reaction conditions using dimedone in the place of HONSu to afford 3a in 53% yield.
5) D. W. Clayton, J. A. Farrington, G. W. Kenner, and J. M. Turner, J. Chem. Soc., 1957, 1398.
6) B. F. Erlanger and E. Brand, J. Am. Chem. Soc., 73, 3508(1951).
7) The elemental analysis of 3c is as follows: Found: C, 56.84; H, 9.09; N, 8.76%. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85%. The different specific rotation value was reported in Ref.8 [$[\alpha]_D^{23}$ +19.3°(MeOH)]. Therefore, the authentic sample of 3c was prepared by condensation of Boc-Leu-OH with H-Gly-OEt using DCCD-HONSu method in 85% yield and compared with 3c itself to confirm the structure.
8) K. Nakajima, O. Okuda, and K. Okawa, "Proceeding of the 14th Symposium on Peptide Chemistry," ed by T. Nakajima, Protein Research Foundation, Osaka(1976), p.17.
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11) R. W. Adamiak and J. Stawinski, Tetrahedron Lett., 1977, 1935; S. Kim and H. Chang, J. Chem. Soc., Chem. Commun., 1983, 1358.

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