Tetrahedron Letters,Vol.28,No.24,pp 2737-2740,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

1-ISOPROPYLALLYLOXYCARBONYL (IPAoc) AS A PROTECTIVE GROUP OF AMINES AND ITS DEPROTECTION CATALYSED BY PALLADIUM-PHOSPHINE COMPLEX

Ichiro MINAMI, Masami YUHARA, and Jiro TSUJI*
Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Summary: As a new protective group of amines, 1-isopropylallyloxycarbonyl (IPAoc) group was developed. IPAoc group can be removed by treatment with a palladium-phosphine catalyst forming carbon dioxide and 4-methyl-1,3-pentadiene by the decarboxylation and β-hydrogen elimination of (π-1-isopropylallyl)-palladium intermediate under neutral conditions. The present protection-deprotection was applied to a one-pot peptide synthesis.

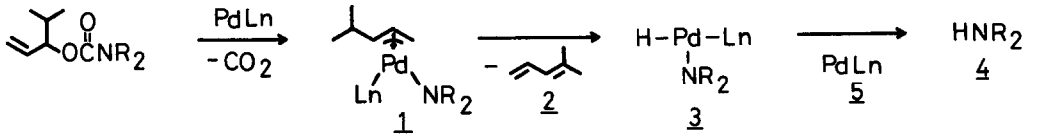
Various protective groups for amines are known and mainly urethane-type protective groups such as benzyloxycarbonyl (Z) and t-butoxycarbonyl (Boc) are widely employed.[1] But even today the development of better protective groups attracts considerable attention. Recently, allyloxycarbonyl group[2-6] as a protective group of amines attracts an interest because it can be cleaved easily by catalysis of palladium-phosphine complexes under mild conditions. The allyloxycarbonyl group is deprotected by the formation of (π-allyl)palladium complex. The critical problem of this deprotection, although it can be carried out under mild conditions, is how to scavenge the allyl group without forming allyl amines. So far two methods are known. In one method, the allyl group is trapped by allylation of reactive carbonucleophiles such as dimedone.[3] Also the allyl group is reduced to propene with some hydride reagents, particularly formic acid[4,5] or silicon hydrides.[6]

We now wish to introduce IPAoc group as a useful new allyl-type protective group. The method of its deprotection is based on the well-known palladium catalyzed 1,3-diene formation from certain allylic compounds.[7] The characteristic feature of this new protective group is its elimination as carbon dioxide and 4-methyl-1,3-pentadiene (**2**) by the decarboxylation and elimination of β-hydrogen from the (π-1-isopropylallyl)palladium intermediate, **1**. Thus the present reaction can be carried out without using nucleophiles or hydride reagents. As shown in Scheme 1, **1** undergoes β-hydrogen elimination to afford **3** and the 1,3-diene **2**. Reductive elimination of **3** gives deprotected amine **4** and regenerates the palladium(0) species **5**.

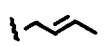
In order to find a new protective group based on the diene forming reaction, at first, we examined the deprotection of N-(2-butenyloxycarbonyl)aniline (**6**). The palladium-catalyzed deprotection in the absence of nucleophiles or hydride reagents proceeded slowly in boiling dioxane to give free aniline in a low yield. At the same time, a considerable amount of N-(2-butenyl)aniline was

obtained as shown in Scheme 2. In order to find a better protective group, 1-isopropylallyloxycarbonyl (IPAoc) group was chosen. The palladium-catalyzed deprotection of N-(1-isopropylallyloxycarbonyl)aniline (7) proceeded in boiling dioxane to give aniline in a nearly quantitative yield. Only a minute amount (2%) of N-allylated product was detected by GLC analysis.

<SCHEME 1>

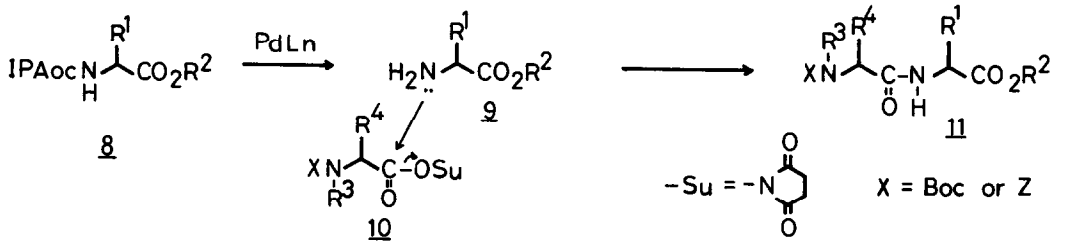


<SCHEME 2>

	PhNHCO$_2$R		PhNH$_2$	PhNHR
6: R= 		dioxane,100°C,6 h	30%	70%
7: R= 	(IPAoc)	dioxane,100°C,15min	98%	2%

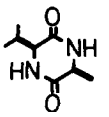
Based on these results, we attempted to prove the usefulness of this protective group in peptide synthesis. At first, IPAoc-Ala-OMe was treated with $Pd_2(dba)_3 \cdot CHCl_3$ [tris(dibenzylideneacetone)dipalladium(chloroform)][8]-PPh_3 catalyst in boiling dioxane. It was confirmed by TLC analysis that the deprotection completed within 30 min. But isolation of pure H-Ala-OMe was somewhat difficult and the isolated yield was unsatisfactory. Then we carried out the deprotection of amino acids in the presence of succinimide esters **10**[5] derived from amino acids as an activated ester, and peptides **11** were obtained in good yields. The reaction corresponds to one-pot synthesis of a peptide bond under neutral conditions. The reaction can be explained by the palladium-catalyzed deprotection of **8** to give free amines **9** and subsequent peptide bond formation with **10** to afford the peptide **11**. In this reaction, N-hydroxysuccinimide is generated as a by-product, which may trap the allyl group of (π-allyl)palladium complex. However, the yield of O-allylated N-hydroxysuccinimide was lower than 20%, showing that the reaction mainly proceeds by β-hydrogen elimination from the (π-allyl)palladium complex **1**.

<SCHEME 3>



As listed in Table 1, the palladium-catalyzed reaction of various IPAoc protected amino acids with succinimide ester gave N-protected peptide esters in

<TABLE 1> ONE-POT SYNTHESIS OF PEPTIDES 11 BY THE PALLADIUM-CATALYZED REACTION OF 8 WITH 10.[a]

RUN	SUBSTRATE[b]	PRODUCT	YIELD(%)	PHYSICAL DATA[c]
1	IPAoc-Ala-OMe Boc-Val-OSu	Boc-Val-Ala-OMe	70	m.p. 134 °C $[\alpha]_D^{25}$ -47.7° (c 1.0, MeOH) (-47.9°)[9]
2	IPAoc-Leu-O^{t}Bu Z-Phe-OSu	Z-Phe-Leu-O^{t}Bu	69	(oil) $[\alpha]_D^{25}$ -26.5° (c 1.4, MeOH) (-27.0°)[10]
3	IPAoc-Ala-Val-OSu		70	m.p. 265-266 °C $[\alpha]_D^{25}$ -27.6° (c 1.0, AcOH) (-27.0°)[9]
4	IPAoc-Ala-Ala-OMe Z-Ala-OSu	Z-Ala-Ala-Ala-OMe	72	m.p. 193-194 °C $[\alpha]_D^{25}$ -91.3° (c 0.5, TFA) (-73.0°)[11]
5	IPAoc-Phe-Met-OMe Z-Ala-OSu	Z-Ala-Phe-Met-OMe	74	m.p.134-136 °C $[\alpha]_D^{20}$ -53.2° (c 1.0, MeOH) (-53.2°)[12]
6	IPAoc-Met-OMe Z-Ala-Phe-OSu	Z-Ala-Phe-Met-OMe	77	m.p. 135-136 °C $[\alpha]_D^{20}$ -53.0° (c 1.0, MeOH)
7	IPAoc-Ala-Leu-OBzl Z-Gly-OSu	Z-Gly-Ala-Leu-OBzl	80	(oil) $[\alpha]_D^{25}$ -31.1° (c 1.0, EtOAc) (-31.6°)[13]
8	IPAoc-Leu-Gly-OEt Boc-Pro-OSu	Boc-Pro-Leu-Gly-OEt	72	(oil) $[\alpha]_D^{25}$ -50.0° (c 1.9, DMF) (-49.2°)[14]

a) Typical procedure (run 1); A solution of Boc-Val-OSu (1 mmol), IPAoc-Ala-OMe (1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mmol), and PPh_3 (0.2 mmol) in dry dioxane (5 mL) was refluxed for 30 min. under argon. Then the reaction mixture was diluted with ethyl acetate (30 mL) and filtered through florisil. The filtrate was evaporated. The product was isolated by recrystallization (ether-pentane). b) IPAoc esters were easily prepared by the reaction of amino acid (10 mmol) with 4,6-dimethyl-2-(1-isopropylallyloxycarbonylthio)pyrimidine (11 mmol) in 90-95% yield.[15] Ala=L-alanine, Phe=L-phenylalanine, Val=L-valine, Met=L-methionine, Leu=L-leucine, Pro=L-proline, Bzl=benzyl, TFA=trifluoroacetic acid. c) Reported data in parentheses.

good yields, and their melting points and optical rotations are in good accordance with reported ones. Other well-known protecting groups of amines or carboxylic acids such as Z or Boc groups and methyl, ethyl, benzyl, t-butyl ester groups are not affected by this reaction. Although palladium(0) species are known to be frequently poisoned by a thio group,[16] the reaction proceeds smoothly with methionine derivatives (runs 5 and 6). When IPAoc-Ala-Val-OSu was employed, cyclic dipeptide (diketopiperazine) was obtained (run 3).

Based on HPLC analysis of Z-Phe-DL-Ala-OMe and the product from the reaction of Z-Phe-OSu and IPAoc-Ala-OMe, it was comfirmed that only L-L form was obtained indicating that no racemization took place during the reaction. This new method is useful for peptide synthesis particularly because the deprotection of **8** and coupling with **10** can be carried out in one-pot under neutral conditions without using any other reagent, and the work-up is very simple. The present reaction is highly chemoselective. When IPAoc-Leu-O^{t}Bu was treated with TFA, IPAoc-Leu-OH was obtained in 94% yield. Furthermore, **12** was recovered almost quantitatively when a mixture of **12** and **13** was treated with 6N HCl. Only Boc group was cleaved in this reaction.

<SCHEME 4>

IPAoc-Ala-OMe (**12**) and Boc-Val-OMe (**13**) —(6N HCl, dioxane)→ **12** (90%) + H-Val-OMe HCl (82%)

ACKNOWLEDGMENT

This research was financially supported by the Grant-in-Aids for Developmental Scientific Research, No. 60850153 and Encouragement of Young Scientists, No. 60790051 from the Ministry of Education, Science and Culture.

REFERENCES

1) T. W. Greene, "Protective Groups in Organic Synthesis", John Willey & Sons, p218 (1981). 2) C. M. Stevens and R. Watanabe, **J. Am. Chem. Soc., 72,** 725 (1950). 3) P. D. Jeffrey and S. W. McCombie, **J. Org. Chem., 47,** 587 (1982). H. Kunz and C. Unverzagt, **Angew. Chem., Int. Ed. Engl. 23,** 436 (1984). 4) I. Minami, Y. Ohashi, I. Shimizu, and J. Tsuji, **Tetrahedron Lett. 26,** 2449 (1985). F. Guibe, O. Dangles, and G. Balavoine, **Tetrahedron Lett., 27,** 2365 (1986). Y. Hayakawa, H. Kato, M. Uchida, H. Kajino, and R. Noyori, **J. Org. Chem., 51,** 2400 (1986). Deprotection by the β-silicon elimination of (π-allyl)-palladium comlex is also known. H. Mastalerz, **J. Org. Chem. 49,** 4092 (1984). 5) H. Kinoshita, K. Inomata, T. Kameda, and H. Kotake, **Chem. Lett., 1985,** 515. 6) L. Birkofer, E. Bierstein, and F. Rutter, **Chem. Ber., 94,** 821 (1961). M. Sakaitani, N. Kurokawa, and Y. Ohfune, **Tetrahedron Lett., 27,** 3753 (1986). 7) J. Tsuji, T. Yamakawa, M. Kaito, and T. Mandai, **Tetrahedron Lett., 1978,** 2075. B. M. Trost, T. R. Verhoeven, and J. M. Fortunak, **Tetrahedron Lett., 1979,** 2301. H. Matsushita and E. Negishi, **J. Org. Chem., 47,** 4161 (1982). 8) T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, and J. A. Ibers, **J. Organometal. Chem., 65,** 253 (1976). 9) D. E. Nitecki, B. Halpern, and J. W. Westley, **J. Org. Chem., 33,** 864 (1968). 10) K. T. Wang and C. H. Li, **J. Org. Chem., 36,** 2419 (1971). 11) M. Goodman, R. Rupp, and F. Naider, **Bioorg. Chem., 1,** 294 (1971). 12) S. Yamada and Y. Takeuchi, **Tetrahedron Lett., 1971,** 3595. 13) N. Izumiya, M. Muraoka, and H. Aoyagi, **Bull. Chem. Soc. Jpn., 44,** 3391 (1971). 14) A. S. Dutta and J. S. Morley, **J. Chem. Soc., C, 1971,** 2896. 15) T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, **Bull. Chem. Soc. Jpn., 46,** 1269 (1973). 16) M. Bodanszky, "Principle of Peptide Synthesis" Springer-Verlag (1984) p184.

(Received in Japan 31 January 1987)