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A NOVEL ROUTE TO DIPEPTIDE AND ITS DERIVATIVE BY MEANS OF THE PALLADIUM CATALYZED FACILE CLEAVAGE OF 1-(1-METHOXYCARBONYL)ALKYL-3-SUBSTITUTED-4-ARYLAZETIDIN-2-ONES

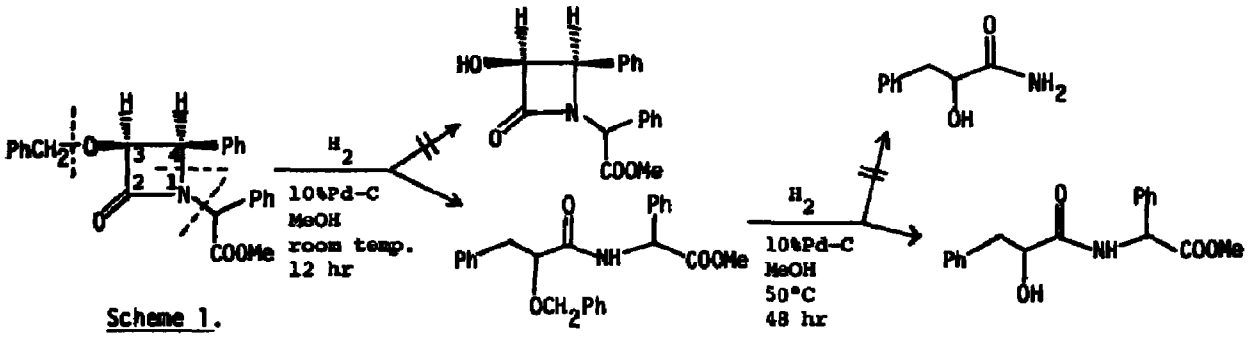
Iwao Ojima*, Shigemi Suga and Rumiko Abe
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229 (Japan)

summary: *1-(1-Methoxycarbonyl)alkyl-3-substituted-4-arylazetidin-2-ones were found to be cleaved exclusively at the N-C^4 bond by the hydrogenolysis on palladium catalyst to give the corresponding dipeptide and its derivative in excellent yields.*

The formation of dipeptides has been extensively studied because of its significance as unit reaction of peptide synthesis.[1] The developed methods of amide linkage formation have been essentially including dehydration from two amino acids, e.g., by means of dicyclohexylcarbodiimide (DCC), activated ester, enzyme or other dehydrating agents.[1] Accordingly, it is of importance to develop newer synthetic methods of peptides without using the conventional dehydrating process. Along this line, we reported quite recently a novel approach to the synthesis of dipeptides using asymmetric hydrogenation of dehydrodipeptides catalyzed by chiral rhodium complexes.[2] On the other hand, we found that 3-azido-4-arylazetidin-2-ones and 3-benzyloxy-4-arylazetidin-2-ones were readily converted to the corresponding amides of α-amino acids and α-hydroxy acids, respectively, by the palladium catalyzed hydrogenolysis.[3] Now, we would like to present here another novel route to dipeptide and its derivative using β-lactams as key-intermediate and also describe the synthesis of dipeptides with excellent optical purity following this novel route.

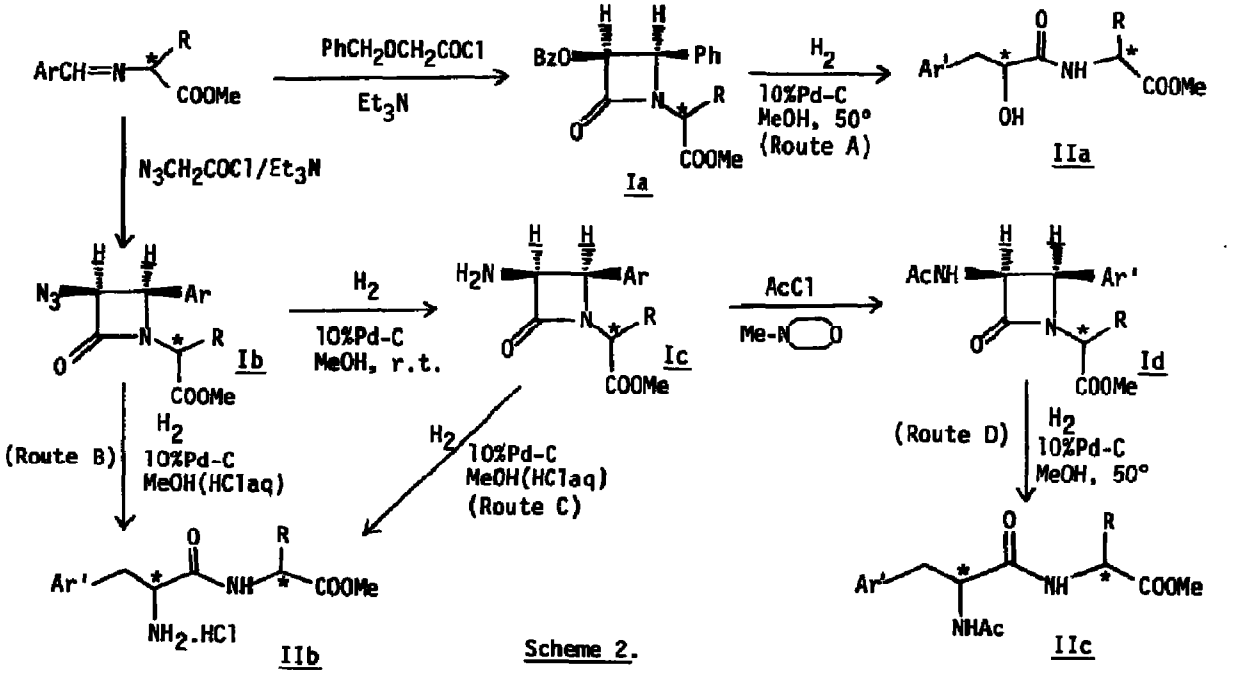
As illustrated in Scheme 2, the key step of the present route is the highly selective and facile cleavage of β-lactam ring. For instance, 1-(1-methoxycarbonyl-1-phenyl)methyl-3-benzyloxy-4-phenylazetidin-2-one (1a-*l*) has three bonds to be cleaved by the palladium catalyzed hydrogenolysis. As it is well known that the cleavage of benzyl-oxygen bond is by far faster than that of benzyl-nitrogen bond,[4] it is reasonable to anticipate that the cleavage of benzyl-oxygen bond is the fastest one. However, to our surprise, the cleavage of β-lactam ring at the benzylic position is much faster than that of benzyl-oxygen bond, and the other benzyl-nitrogen bond remains intact as expected, as shown in Scheme 1. The result clearly indicates that the ring strain of β-lactam greatly accelerates the cleavage.

The relative easiness of the cleavage of β-lactam ring vs. that of benzyl-oxygen bond is, of course, affected by the substituent(s) on nitrogen and phenyl group at C^4, and sometimes the formation of 3-hydroxyazetidin-2-one could be observed. In the case of 3-azidoazetidin-2-ones, the reduction of azido group to amine always prevails over the cleavage of β-lactam ring. Thus, 3-aminoazetidin-2-one was obtained as initial product in excellent yield in every case.



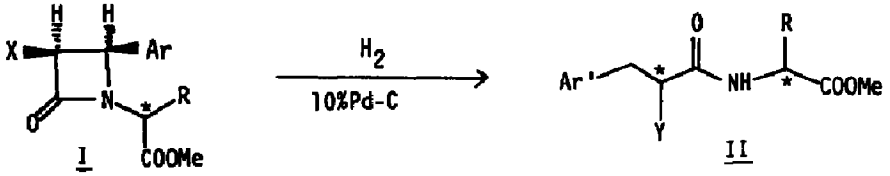
Scheme 1.

Scheme 2 illustrates the general formula of the synthesis of dipeptide and its derivative. β-Lactams, Ia and Ib, are readily prepared in good to excellent yields by using modified Bose's method[5] from the Schiff bases of α-amino esters and benzyloxyacetyl chloride or azidoacetyl chloride in the presence of triethylamine in methylene chloride. The β-lactams thus obtained are submitted to hydrogenolysis on palladium catalyst via Route A∿D to give the corresponding dipeptides, IIa, IIb and IIc, in excellent yields. As the free dipeptide esters are rather labile because of its considerably strong basicity, we isolated those as hydrogen chloride salt, IIb, or as N-acetyl derivative, IIc. Results are shown in Table 1. As to the stereochemistry of the C^3 and C^4 position, only cis isomer was found to be formed in every case examined (J = 4.5 ∿ 5.5 Hz).



Scheme 2.

Table 1. Synthesis of Dipeptides



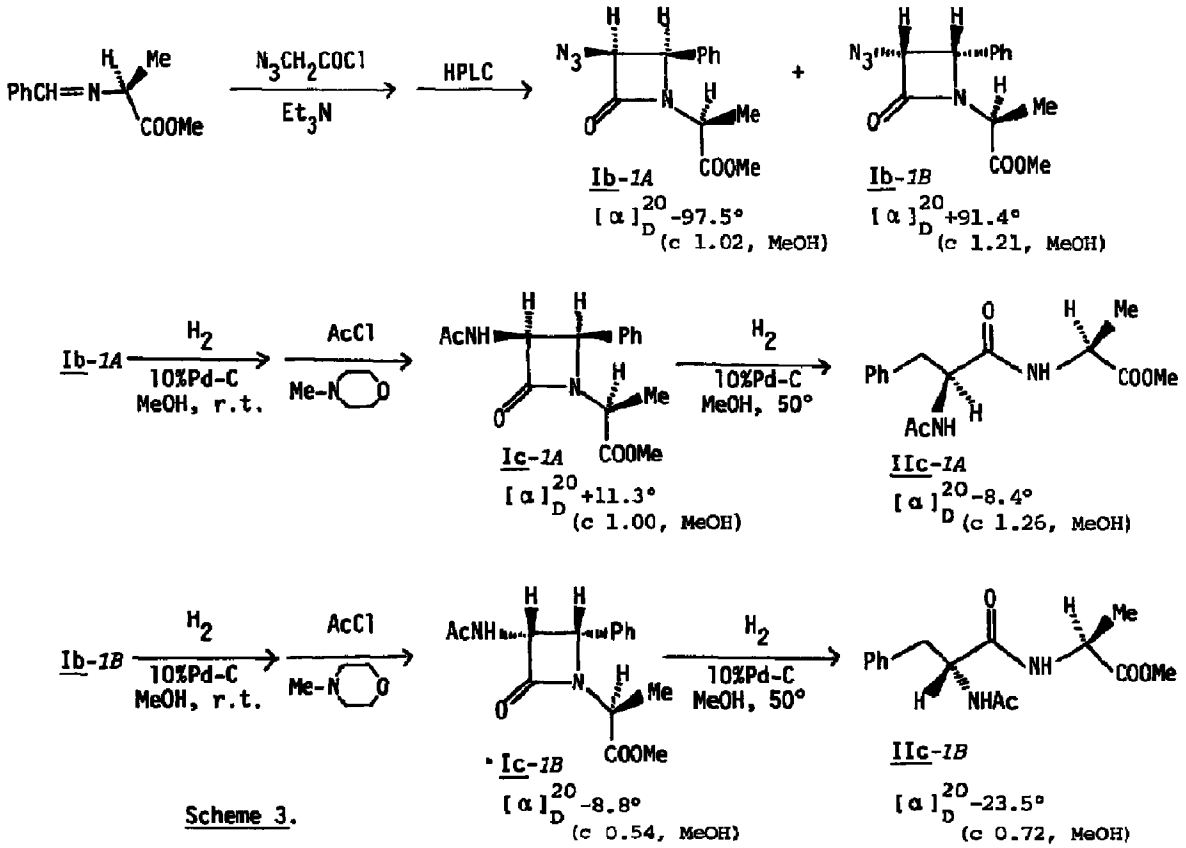
Entry	β-Lactam (I) X	R	Ar	Yield(%)	Dipeptide (II) Y	R	Ar'	Yield(%)	Route
1	N_3(AcNH)	Ph	Ph	88 (80)[a]	AcNH	Ph	Ph	90	D
2	N_3(AcNH)	^{i}Pr	Ph	74 (85)[a]	AcNH	^{i}Pr	Ph	92	D
3	N_3(AcNH)	Me	Ph	75 (82)[a]	AcNH	Me	Ph	97	D
4	N_3(AcNH)	CH_2Ph	Ph	88 (87)[a]	AcNH	CH_2Ph	Ph	93	D
5	N_3	Ph	p-Z-O-C_6H_4[b]	90	NH_2.HCl	Ph	p-HO-C_6H_4	98	B
6	$PhCH_2O$	Ph	Ph	92	OH	Ph	Ph	88	A
7	$PhCH_2O$	^{i}Pr	Ph	81	OH	^{i}Pr	Ph	94	A
8	$PhCH_2O$	Me	Ph	93	OH	Me	Ph	89	A
9	$PhCH_2O$	CH_2Ph	Ph	72	OH	CH_2Ph	Ph	98	A
10	$PhCH_2O$	Ph	p-Z-O-C_6H_4[b]	80	OH	Ph	p-HO-C_6H_4	89	A
11	$PhCH_2O$	Ph	3,4-$(BzO)_2C_6H_3$[c]	91	OH	Ph	3,4-$(HO)_2C_6H_3$	98	A

[a] Yield based on Ib. [b] Z = benzyloxycarbonyl [c] Bz = benzyl

Next, we performed the synthesis of dipeptides with excellent optical purity using the present method. The synthesis of (S,S)-Ac-Phe-Ala-OMe and (R,S)-Ac-Phe-Ala-OMe is typically described (See, Scheme 3). 1-(1-Methoxycarbonyl)ethyl-3-azido-4-phenylazetidin-2-one (Ib-*1*) was obtained in 75% yield by the reaction of benzylidene[(S)-1-methoxycarbonyl]ethylamine with azidoacetyl chloride in methylene chloride at 0°C ∿room temperature. (Ib-*1*) was a mixture of two diastereomers, Ib-*1A* (J_{AB} = 5.0 Hz on adding $Eu(fod)_3$)[6] and Ib-*1B* (J_{AB} = 5.5 Hz). The mixture was submitted to high pressure liquid chromatography (HPLC) on a Waters System 500 using n-hexane-ethyl acetate (4:1) as eluent to give pure Ib-*1A* (46%) and Ib-*1B* (54%) in virtually quantitative yield. Then, each separated β-lactam was converted to the corresponding dipeptide, IIc-*1A* or IIc-*1B*, in 80-85% yield, and IIc-*1A* was turned to be (S,S)-Ac-Phe-Ala-OMe based on either the comparison of specific optical rotation, IR and NMR spectra with those of an authentic sample or HPLC analysis. The HPLC analysis also revealed that the optical purity of either (S,S)-Ac-Phe-Ala-OMe (IIc-*1A*) or (R,S)-Ac-Phe-Ala-OMe (IIc-*1B*) was >99.5%.

Although the present reaction is applicable only to the synthesis of dipeptide and its derivative bearing a β-aromatic α-amino acid or a β-aromatic α-hydroxy acid moiety at this stage, it surely serves as unique and a convenient route to these compounds without using a conventional dehydrating process.

Further investigations on expanding this type of cleavage to non-benzylic systems and on the application of this reaction to the synthesis of tripeptides and tetrapeptides are actively underway.



Scheme 3.

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References and Notes

1. e.g., J. C. Sheehan and G. P. Hess, J. Am. Chem. Soc., 77, 1067 (1955); Idem, ibid., 78, 1367 (1956); G. W. Anderson, J. E. Zimmerman and F. M. Callahan, ibid, 86, 1839 (1964); R. B. Woodward, R. A. Olofson and H. Mayer, ibid., 83, 1010 (1961); H. A. Staab, Ann., 609, 75 (1957); J.C. Sheehan, J. Preston and P. A. Cruickshank, J. Am. Chem. Soc., 87, 2492 (1965); Y. Isowa, M. Ohmori, M. Sato and K. Mori, Bull. Chem. Soc. Jpn., 50, 2766 (1977) and references therein.

2. I. Ojima and T. Suzuki, Tetrahedron Lett., 1239 (1980).

3. I. Ojima, S. Suga and R. Abe, Chem. Lett., 853 (1980). We also have found that other catalysts such as Pt-C, Ru-C, Rh-C, $PdCl_2$ and $(PhCN)_2PdCl_2$ are virtually ineffective for the reaction.

4. e.g., M. Freifelder, "Practical Catalytic Hydrogenation," Weiley-Interscience, New York, 1971, pp 398-445.

5. e.g., A. K. Bose, M. S. Manhas, J. C. Chib, H. P. S. Chawla and B. Dayal, J. Org. Chem., 39, 2877 (1974).

6. The ^1H nmr spectrum of this compound showed a singlet at δ 4.94 ppm unless $Eu(fod)_3$ was added because of the coincidence of the chemical shifts of two protons. However, a well separated AB quartet (J_{AB} = 5.0 Hz) appeared on adding $Eu(fod)_3$.

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