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# A NEW AND CONVENIENT ROUTE TO THE AMIDES OF α-AMINO ACIDS AND α-HYDROXY ACIDS BY MEANS OF THE PALLADIUM CATALYZED FACILE CLEAVAGE OF 3-SUBSTITUTED-4-ARYLAZETIDIN-2-ONES

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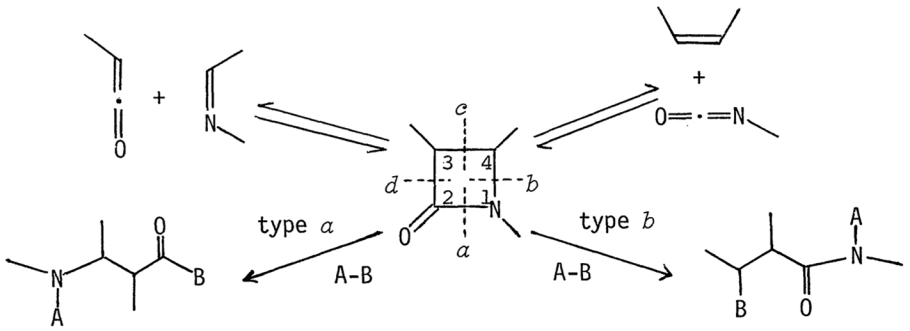
3-Substituted-4-arylazetidin-2-ones were found to be cleaved selectively at the N-$C^4$ bond by the hydrogenolysis on palladium catalyst to give the corresponding amides of α-amino acids or α-hydroxy acids in excellent yields.

Although the synthesis of β-lactams has been extensively studied for a long time in connection with the naturally occurring β-lactam antibiotics,[1] little attention has been focused on the usage of β-lactams as synthetic intermediate. It is well known that the cleavage of β-lactam ring takes place usually at the N-C(O) bond (type *a*) by nucleophilic reagents including water.[2] However, there are also other types of cleavage possible to occur, e.g., cleavage at N-$C^4$, $C^3$-$C^4$, $C^2$-$C^3$ or metathesis:[2]




(1)

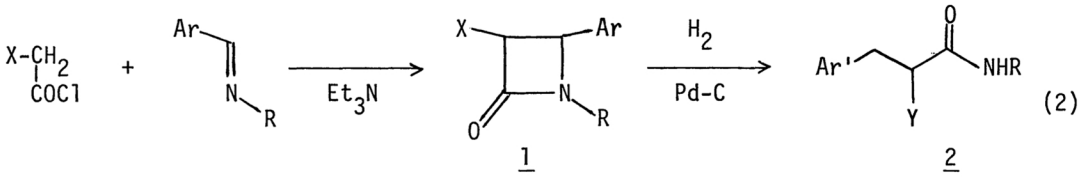
Among these possibilities, we have found that the cleavage of N-$C^4$ bond (type *b*) proceeds exclusively in a palladium catalyzed hydrogenolysis when an aryl substituent is attached to $C^4$ position.[3] As 3-substituted-4-arylazetidin-2-ones can easily be synthesized by the cycloaddition of Schiff base with ketene which is generated in situ from acyl chloride and triethylamine,[1,4] the type *b* cleavage can serve as new synthetic route to functionalized amides. Now, we describe here a new and convenient route to the amides of α-amino acids and α-hydroxy acids by means of the type *b* cleavage of 3-azido-4-arylazetidin-2-ones and 3-benzyloxy-4-arylazetidin-2-ones.

3-Azido-4-arylazetidin-2-ones or 3-benzyloxy-4-arylazetidin-2-ones were readily prepared in good to excellent yields by using Bose's method[4] with some modification from Schiff bases and azidoacetyl chloride or benzyloxyacetyl chloride in the presence of triethylamine in methylene chloride. The β-lactams thus obtained were submitted to hydrogenolysis on palladium catalyst to

Table 1. Synthesis of the Amides of α-Amino Acids and α-Hydroxy Acids by the Palladium Catalyzed Novel Cleavage of β-Lactams[a]

| Entry | Ar' | R | Y | Conditions | Isolated Yield(%) |
|---|---|---|---|---|---|
| 1 | 3,4-$(MeO)_2C_6H_3$ | Ph | $NH_2$ | 50°C, 15 hr | 97 |
| 2 | | | OH | 50°C, 36 hr | 98 |
| 3 | 3,4-$(MeO)_2C_6H_3$ | $CHMe_2$ | $NH_2$ | 50°C, 48 hr | 95 |
| 4 | | | OH | 50°C, 39 hr | 97 |
| 5 | 3,4-$(MeO)_2C_6H_3$ | $(CH_2)_2CO_2Et$ | $NH_2$ | 50°C, 40 hr | 95 |
| 6 | | | OH | 50°C, 15 hr | 96 |
| 7 | 3,4-$(MeO)_2C_6H_3$ | CHMePh | $NH_2$ | 50°C, 87 hr | 94 |
| 8 | 3,4-$(HO)_2C_6H_3$[b] | Ph | $NH_2$ | 50°C, 87 hr[e] | 95 |
| 9 | 3,4-$(CH_2O_2)C_6H_3$ | Ph | $NH_2$ | 25°C, 16 hr[e] | 98 |
| 10 | 4-F-$C_6H_4$ | Ph | $NH_2$ | 50°C, 43 hr[e] | 97 |
| 11 | | | OH | 50°C, 15 hr[e] | 99 |
| 12 | 4-HO-$C_6H_4$[c] | Ph | $NH_2$ | 50°C, 46 hr[e] | 91 |
| 13 | | | OH | 50°C, 15 hr[e] | 94 |
| 14 | Indol-3-yl[d] | Ph | $NH_2$ | 50°C, 24 hr[e] | 98 |
| 15 | | | OH | 50°C, 21 hr[e] | 98 |
| 16 | Pyridin-2-yl | Ph | $NH_2$ | 50°C, 17 hr[e] | 97[f] |
| 17 | Furan-2-yl | Ph | $NH_2$ | 25°C, 7 hr | 62[g] |

[a] All reactions were run with 1.0 mmol of β-lactam and 50-580 mg of 10% Pd-C in 30-60 ml of ethanol under an atmospheric pressure of hydrogen unless otherwise noted. [b] Ar = 3,4-bis-(benzyloxycarbonyl)phenyl. [c] Ar = 4-benzyloxycarbonylphenyl. [d] Ar = 1-benzyloxycarbonyl-indol-3-yl. [e] Tetrahydrofuran was used as co-solvent. [f] The amide contained a trace amount of side product, an aromatic ring of which was hydrogenated. [g] Isolated by a column chromatography on silica gel. A side product, N-phenyl-2-amino-3-(tetrahydrofuran-2-yl)propionamide, was also formed (30%).



(2)

1

a) X = $N_3$, Y = $NH_2$
b) X = $PhCH_2O$, Y = OH

give 3-aryl-2-aminopropionamides or 3-aryl-2-hydroxypropionamides in excellent yields.

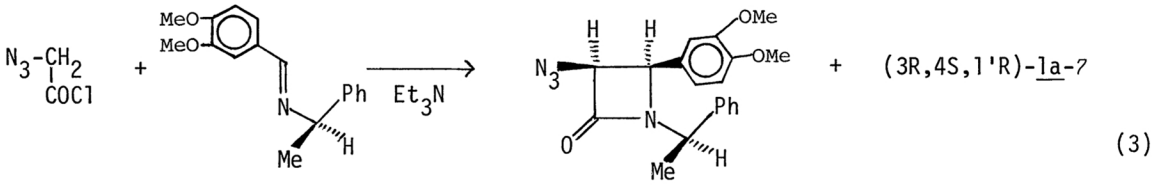
In a typical experiment, a mixture of 1-phenyl-3-azido-4-(3,4-dimethoxyphenyl)azetidin-2-one (300 mg) and 10% Pd-C (230 mg) in 50 ml of ethanol was placed in a usual hydrogenation apparatus, and the mixture was stirred at 50°C and 1 atm of hydrogen for 15 hr. The completion of the hydrogenolysis was checked by hydrogen absorption and thin layer chromatography. After the catalyst was filtered off and the solvent was evaporated, 269 mg (97%) of N-phenyl-2-amino-3-(3,4-dimethoxyphenyl)propionamide (2a-*1*) was obtained as colorless crystals: mp. 72-74°C.

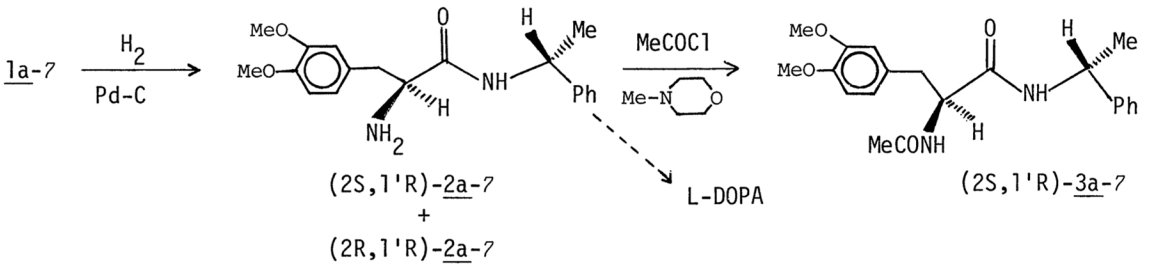
Results on using a variety of 3-azido-4-arylazetidin-2-ones and 3-benzyloxy-4-arylazetidin-2-ones are listed in Table 1. With regard to the synthesis of aromatic α-amino acids, Erlenmeyer's method[5] is the most commonly used device, which involves i) formation of azlactone, ii) hydrolysis to N-acyldehydro-α-amino acid, iii) reduction giving N-acyl-α-amino acid, and iv) hydrolysis leading to α-amino acid. On the other hand, the present method involves i) formation of β-lactam, ii) hydrogenolysis giving α-aminocarboxamide, and iii) hydrolysis leading to α-amino acid. In addition, the present method is readily applicable to the synthesis of α-hydroxycarboxamides and α-hydroxy acids. Accordingly, the present reaction provides an effective and convenient route to the amides of aromatic α-amino acids and α-hydroxy acids such as DOPA, p-fluorophenylalanine, tryptophan, phenyllactic acid etc., as shown in Table 1.

As to the stereochemistry of the $C^3$ and $C^4$ position, it turned out that only cis isomer was formed for every 3-azido-4-arylazetidin-2-one examined whereas a mixture of cis and trans isomer was produced sometimes for 3-benzyloxy-4-arylazetidin-2-ones (1b-*2*: cis/trans = 90/10; 1b-*15*: cis/trans = 61/39; others: all cis).

We also carried out the asymmetric synthesis of α-aminocarboxamide using (3,4-dimethoxyphenyl)methylidene-(R)-1-phenylethylamine (Entry *7*) (eqn. 3). The extent of chirality transfer was found to be 40%: (3S,4R,1'R) isomer was preferably produced. The hydrogenolysis of the obtained β-lactam afforded N-[(R)-1-phenylethyl]-2-amino-3-(3,4-dimethoxyphenyl)propionamide (2a-*7*) in 94% yield: (2S,1'R)/(2R,1'R) = 70/30. The two diastereomers were readily separated by column chromatography on silica gel. The stereochemistry at $C^2$ position was determined by the correlation with an authentically prepared[6] (2S,1'R)-N-(1-phenylethyl)-2-acetylamino-3-(3,4-dimethoxyphenyl)propionamide (3a-*7*) based on NMR spectroscopy and thin layer chromatography on silica gel.

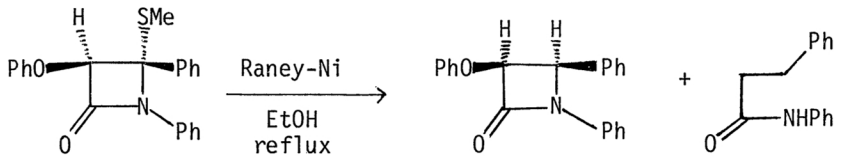
As Table 1 (Entry *5* and *6*) shows, the present reaction is applicable to the synthesis of dipeptide and depsidipeptide. Further results along this line will be reported in the near future.




## REFERENCES AND NOTES


1. e.g., A. K. Mukerjee and R. C. Srivastava, Synthesis, 327 (1973); N. S. Isaaks, Chem. Soc. Rev., 5, 181 (1976); A. K. Mukerjee and A. K. Singh, Tetrahedron, 34, 1731 (1978).
2. Th. Wieland in "METHODEN DER ORGANISCHEN CHEMIE, BAND XI/2," Edtd. by E. Müller, Georg Thieme Verlag, Stuttgart, 1958, pp 518-528.
3. The type *b* cleavage of β-lactam ring by Raney-Ni was described in the case of 1,4-diphenylazetidin-2-one.[2] However, Raney-Ni was found to be too strong reagent to obtain the corresponding amide of which functional group(s) remains intact [A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, Tetrahedron Lett., 2823 (1972)]:




4. e.g., A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla, and B. Dayal, J. Org. Chem., 39, 2877 (1974).
5. e.g., E. Erlenmeyer and J. T. Halsey, Ber., 30, 2981 (1897).
6. Authentic sample of (2S,1'R)-3a-7 was prepared by the condensation of (S)-N-acetyl-3,4-dimethoxyphenylalanine with (R)-1-phenylethylamine using dicyclohexylcarbodiimide and 1-hydroxybenztriazole in dimethylformamide.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