# Communications to the Editor

[Chem. Pharm. Bull. 33(4)1749—1751(1985)]

## A NOVEL SYNTHESIS OF L-ω-CARBAMOYL-α-AMINO ACIDS FROM L-α,ω-DIAMINO ACIDS BY RUTHENIUM TETROXIDE OXIDATION METHOD

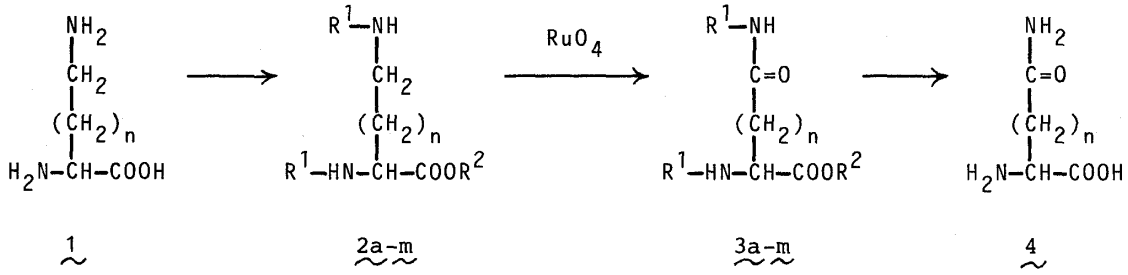
Shigeyuki Yoshifuji,* Ken-ichi Tanaka, and Yoshihiro Nitta
School of Pharmacy, Hokuriku University,
Kanagawa-machi Ho-3, Kanazawa 920-11, Japan

The oxidation of N,C-protected L-2,4-diaminobutyric acid, L-ornithine and L-lysine with $RuO_4$ gave the corresponding L-asparagine, L-glutamine and L-2-aminoadipic acid 6-amide derivatives, respectively.

KEYWORDS ——— ruthenium tetroxide oxidation; amide synthesis; L-amino acid synthesis; carboxamide N-protection; ruthenium tetroxide; L-α,ω-diamino acid; L-ω-carbamoyl-α-amino acid

Ruthenium tetroxide ($RuO_4$) is a powerful oxidizing agent,[1] and in recent years it has been especially used for the oxidation of some cyclic amines to the corresponding lactams or cyclic imides.[2,3,4] On the other hand, $RuO_4$ oxidant has been claimed to be not applicable to the oxidation of straight-chain alkylamine which was initially investigated by Berkowitz and Rylander,[5] who obtained only an intractable mixture. On the analogy of the oxidation of cyclic amine, N-protection with acyl group seems to be effective to produce the diacyl compound. However, to date no systematic study on the $RuO_4$ oxidation of N-acylated alkylamines has appeared. Besides making such a systematic study,[6] we applied this to oxidative transformation of L-α-amino acids possessing side chain alkylamino group. Here we wish to report the chemical conversion of L-2,4-diaminobutyric acid, L-ornithine and L-lysine, involving the $RuO_4$ oxidation of N,C-protected derivatives of these amino acids as shown in Chart 1.

The existing procedure[2,3,7] for the $RuO_4$ oxidation was greatly improved with our method for this work. As N-protecting group, tert-butoxycarbonyl (Boc) and trichloroethoxycarbonyl (Troc) groups, and as carboxyl masking function, tert-butyl and p-nitrobenzyl (NBzl) groups were also chosen for easy deprotection after the oxidation. For an organic solvent under the two-phase system of the $RuO_4$ oxidation, ethyl acetate was employed instead of the traditional chlorinated methane (carbon tetrachloride or chloroform) or the new solvent system[8] developed by Sharpless for the oxidation of non-nitrogen compounds, and our ethyl acetate was found to be superior in enhancing both the solubility of the substrates and the rate of reaction. Thus, as a typical example, N,N'-diBoc-L-ornithine NBzl ester (2d: 2 mmol) was oxidized in ethyl acetate (40 ml) with a small amount of $RuO_2$ hydrate (120 mg) in combination with excess 10% aqueous sodium metaperiodate (120 ml) under vigorous




1 2a-m 3a-m 4

$R^1$,$R^2$: protecting group (see Table I)

1 : n=1: L-2,4-diaminobutyric acid; n=2: L-ornithine, n=3: L-lysine

Chart 1

Table I. Oxidation of N,C-Protected Diamino Acids with $RuO_4$

| Substrate 2 | n | $R^1$ | $R^2$ | Reaction time (h) | Product(3a-m) yield (%) | $[\alpha]_D^{25}$ (c=1,$CHCl_3$) | $^{13}$C-NMR(C=O)[a] δ(ppm) |
|---|---|---|---|---|---|---|---|
| a | 1 | Boc | NBzl | 10 | 84 | +22.4° | 173.0 |
| b | | | Me | 10 | 79 | +26.5° | 173.0 |
| c | 2 | Boc | tert-Bu | 6 | 54 | +2.4° | 174.0 |
| d | | | NBzl | 24 | 73 | +1.1° | 174.0 |
| e | | | Me | 5 | 72 | +7.7° | 174.1 |
| f | | Troc | NBzl | 96 | 72 | +1.6° | 173.5 |
| g | | | Me | 120 | 72 | +6.8° | 173.7 |
| h | 3 | Boc | tert-Bu | 6 | 85 | +1.0° | 174.3 |
| i | | | NBzl | 8 | 84 | +3.8° | 174.2 |
| j | | | Me | 5 | 79 | +9.6° | 174.4 |
| k | | Troc | tert-Bu | 35 | 83 | +2.6° | 173.8 |
| l | | | NBzl | 50 | 79 | +3.2° | 173.8 |
| m | | | Me | 120 | 81 | +8.3° | 173.8 |

Boc = tert-butoxycarbonyl; Troc = trichloroethoxycarbonyl; NBzl = p-nitrobenzyl.
a) Measured in $CDCl_3$; C=O carbon: imide C=O produced by the oxidation.

stirring at room temperature for 24 h. The crude product obtained from the organic phase was purified by silica-gel column chromatography to afford N,N'-diBoc-L-glutamine NBzl ester (3d) in 73% yield. Results for all oxidations are summarized in Table I. The oxidation products (3a-m), which are all new compounds, were characterized on the basis of their analytical and spectral data: carbon-13 NMR spectra ($^{13}$C-NMR in Table I) were most helpful to detect the imide carbonyl function newly introduced.

Now, three representative products (3a,c,h) were converted to free amino acids (4) by appropriate deprotection reactions commonly used in amino acid chemistry.[9] Two amino acids obtained from 3a and 3c were identified with authentic L-asparagine and L-glutamine, respectively. One derived from 3h was further hydrolyzed to amino dicarboxylic acid, which was identified with L-2-aminoadipic acid. It was found that the chirality at the α-position of the starting amino acids was not disturbed during the course of the oxidation.

The present chemical conversion provides an efficient and general synthetic route to optical active α-amino acids possessing protected (3a-m type) or unprotected carbamoyl group from L-α,ω-diamino acids, which may be useful in amino acid and peptide syntheses.[10]

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(Received February 12, 1985)