

Cleavage of NH₂ Terminal Tyrosyl–Peptide Bonds using Hypervalent Iodine

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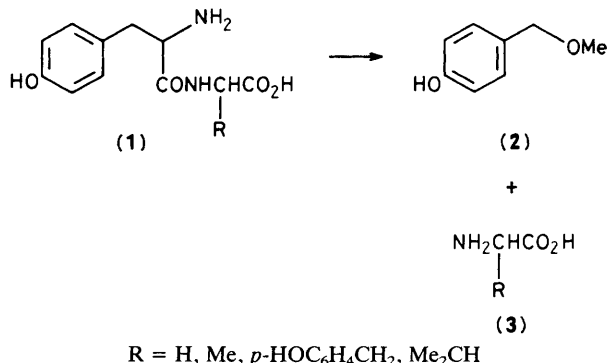
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The cleavage of NH₂-tyrosine dipeptides with C₆H₅I(OAc)₂–MeOH–KOH yields 4-(methoxymethyl)phenol.

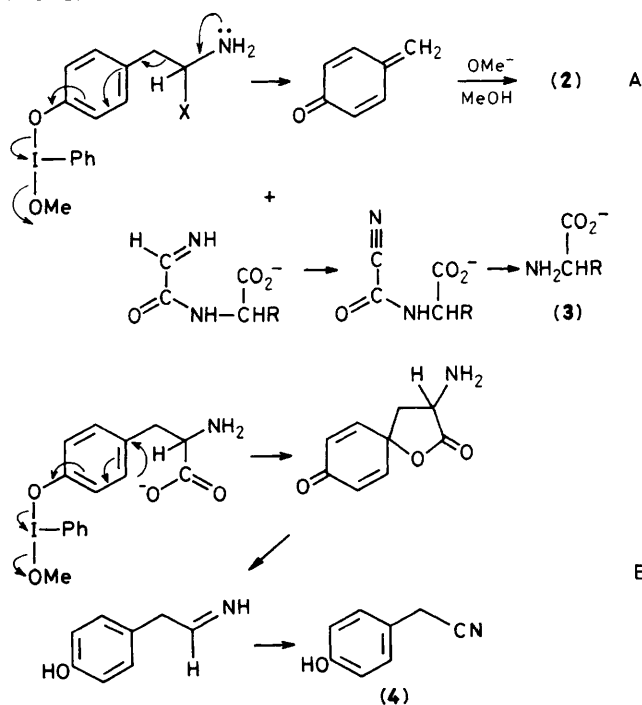
We report a specific cleavage reaction of NH₂-terminal tyrosyl peptides as expressed in Scheme 1 and summarised in Table 1.

The dipeptides L-tyrosyl-L-alanine, L-tyrosylglycine, L-tyrosyl-L-tyrosine, and L-tyrosyl-L-valine, Table 1, entries 1–4, respectively, gave 4-(methoxymethyl)phenol (2)¹ in high yield under the conditions indicated in Scheme 1. The fact that L-alanyl-L-tyrosine, entry 5, Table 1, does not yield (2) indicates the specific nature of the NH₂-terminal cleavage. Similarly, L-tryptophyl-L-tyrosine, entry 6, Table 1, undergoes fragmentation to yield 3-methoxymethyl-3H-indole in a cleavage reaction characteristic of an NH₂-terminal dipeptide.²

In order to define a mechanism for these reactions, it is relevant that *p*-hydroxyphenylethylamine undergoes cleavage to yield (2) but *p*-methoxyphenylethylamine does not,



Scheme 1. Reagents and conditions: PhI(OAc)₂, KOH–MeOH, 0–5 °C.



Scheme 2

entries 7 and 8, Table 1, respectively. Also 3,4-methylenedioxyamphetamine does not yield (2), entry 9. This indicates the necessity of the phenolic hydroxy group. L-Phenylalanine does not react under these conditions. Furthermore L-tyrosine does not yield (2) but rather 4-hydroxybenzyl cyanide (4). L-Tyrosinamide also yields (4).

We propose initial ligand exchange³ involving the phenolic hydroxy group and PhI(OMe)₂ formed *in situ*,⁴ followed by reductive elimination of PhI. This may occur *via* fragmentation with NH₂ providing the electron source, pathway A, Scheme 2, or *via* intramolecular participation, pathway B, Scheme 2.

Pathway A leading to (2) *via* the presumed intermediacy of 4-methylenecyclohexadienone is followed in examples in which a good intramolecular nucleophile is not present. This is the case in the peptide systems, X = CONR, and tyramine, X = H. In cases where X = CO₂[–] or CONH₂, intramolecular lactone formation accompanied by reductive elimination may occur (pathway B). Subsequent oxidative fragmentation yields 4-hydroxybenzyl cyanide (4).^{5,6} In the peptide systems the amino acid moiety (3) results from presumed oxidative fragmentation to an acyl cyanide followed by hydrolysis and decarboxylation of the carbamic acid. L-Alanyl-L-tyrosine does not yield (2) possibly indicating that acylation on nitrogen reduces the driving force for cleavage supplied by the amino nitrogen. The carboxylate group should be capable of participation in this system but fragmentation to 4-hydroxybenzyl cyanide cannot occur.

L-Tyrosine constitutes the *N*-terminus of the analgesic peptides enkephalin⁷ and human-β-endorphin⁸ and is considered to be essential for activity. Oxidative cleavage of

Table 1. Cleavage reaction of tyrosyl derivatives using hypervalent iodine.^{a,b}

| Entry | Compound | Product | Yield/% |
|-------|---|-------------------------|---------|
| 1 | L-Tyrosyl-L-alanine | (2) ^c | 71 |
| 2 | L-Tyrosylglycine | (2) | 62 |
| 3 | L-Tyrosyl-L-tyrosine | (2) | 78 |
| 4 | L-Tyrosyl-L-valine | (2) | 65 |
| 5 | L-Alanyl-L-tyrosine | (2) | 0 |
| 6 | L-Tryptophyl-L-tyrosine | 3-(methoxymethyl)indole | 62 |
| 7 | Tyramine (<i>p</i> -hydroxyphenylethylamine) | (2) | 65 |
| 8 | <i>p</i> -Methoxyphenylethylamine | [(2)] | 0 |
| 9 | 3,4-Methylenedioxyamphetamine | [(2)] | 0 |
| 10 | L-Phenylalanine | [(2)] | 0 |
| 11 | L-Tyrosine | (4) | 52 |
| 12 | L-Tyrosinamide | (4) | 61 |

^a Cleavage procedure: KOH (30 mmol) was dissolved in MeOH (50 ml) and cooled to 0 °C. L-Tyrosine (6 mmol) was added to the stirred solution. PhI(OAc)₂ was added over a period of 1.5 h and stirring was continued for 1.5 h. The reaction mixture was then acidified and the product was isolated by extraction with CHCl₃. Recrystallization from Et₂O–hexane (1 : 1) gave (2) or (4). ^b The dipeptides were shown to be stable under the reaction conditions in the absence of PhI(OAc)₂. ^c M.p. 76–79 °C, lit. 83–86 °C, ref. 1.

tyrosyl units in peptides has been reported but NH_2 -terminal tyrosine peptides failed to undergo the expected cleavage with *N*-bromosuccinimide.⁹ Cleavage of tyrosyl proteins using *O*-iodosylbenzoic acid has been claimed¹⁰ but apparently this is in fact a positive halogen process.¹¹

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References

- 1 W. G. Galetto and P. G. Hoffman, *J. Agric. Food Chem.*, 1978, **26**, 195.
- 2 R. M. Moriarty and M. Sultana, *J. Am. Chem. Soc.*, accepted for publication.
- 3 R. L. Amey and J. C. Martin, *J. Am. Chem. Soc.*, 1979, **101**, 5294.
- 4 B. C. Schardt and C. L. Hill, *Inorg. Chem.*, 1983, **22**, 1563.
- 5 Z. Eckstein and E. Grochowski, *Przem. Chem.*, 1959, **38**, 614; *Chem. Abstr.*, 1960, **54**, 16422b.
- 6 G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, and R. H. Boutin, *J. Org. Chem.*, 1984, **49**, 4272. These authors have observed the formation of benzyl cyanide from the reaction of α -phenylglycine with $\text{PhI}(\text{OCOCF}_3)_2$ in pyridine.
- 7 J. Hughes, *Brain Res.*, 1975, **88**, 295.
- 8 R. Guillemin, N. Ling, and R. Burgus, *C.R. Hebd. Seances Acad. Sci., Ser. D*, 1976, **282**, 783.
- 9 M. Wilchek and B. Witkop, *Biochem. Biophys. Res. Commun.*, 1967, **26**, 296.
- 10 W. C. Mahoney, P. K. Smith, and M. A. Hermodson, *Biochemistry*, 1981, **20**, 443.
- 11 A. Fontana, D. Dalzoppo, C. Grandi, and M. Zamboni, *Biochemistry*, 1981, **20**, 6997.