# Cleavage of $NH_2$ Terminal Tyrosyl–Peptide Bonds using Hypervalent Iodine

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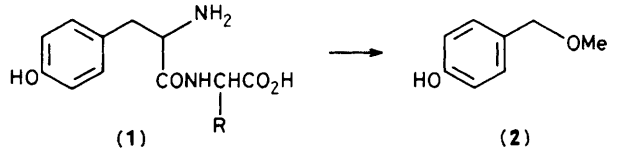
The cleavage of $NH_2$-tyrosine dipeptides with $C_6H_5I(OAc)_2$–MeOH–KOH yields 4-(methoxymethyl)phenol.



We report a specific cleavage reaction of $NH_2$-terminal tyrosyl peptides as expressed in Scheme 1 and summarised in Table 1.

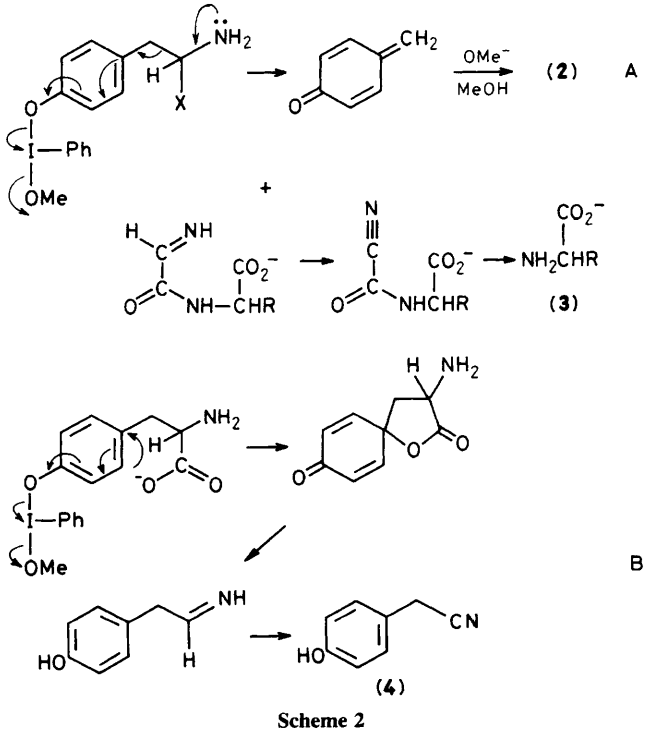
The dipeptides L-tyrosyl-L-alanine, L-tyrosylglycine, L-tyrosyl-L-tyrosine, and L-tyrosyl-L-valine, Table 1, entries 1—4, respectively, gave 4-(methoxymethyl)phenol (**2**)[1] in high yield under the conditions indicated in Scheme 1. The fact that L-alanyl-L-tyrosine, entry 5, Table 1, does not yield (**2**) indicates the specific nature of the $NH_2$-terminal cleavage. Similarly, L-tryptophyl-L-tyrosine, entry 6, Table 1, undergoes fragmentation to yield 3-methoxymethyl-3*H*-indole in a cleavage reaction characteristic of an $NH_2$-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,




R = H, Me, *p*-$HOC_6H_4CH_2$, $Me_2CH$

**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 exchange[3] 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 $NH_2$ 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 = $CO_2^-$ or $CONH_2$, 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 enkephalin[7] and human-β-endorphin[8] 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 (*p*-hydroxyphenylethylamine) | (**2**) | 65 |
| 8 | *p*-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 $CHCl_3$. Recrystallization from $Et_2O$–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 claimed[10] but apparently this is in fact a positive halogen process.[11]

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