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SELECTIVE MODIFICATION OF GLYCINE RESIDUES IN DIPEPTIDES

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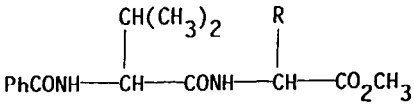
Summary: Reaction of dipeptides with N-bromosuccinimide results in selective α-bromination of glycine residues. Subsequent reactions of brominated peptides with diethyl malonate and allyltributyltin afford the diethyl malonyl- and allyl-substituted glycine derivatives, respectively.

A number of methods for the synthesis of amino acids involve ionic reactions in the elaboration of α-halogenated glycine derivatives.[1-4] With peptides these methods have been applied only to the modification of C-terminal glycine residues in dipeptides.[2,3] This restriction may be attributed, at least in part, to a lack of methods for the synthesis of peptides with an α-halogenated glycine residue at other than the C-terminal position. In the present work, which is based on our recent study of the preferential reaction of glycine residues in reactions of amino acid derivatives with N-bromosuccinimide,[5] we describe the direct and selective α-bromination of N- and C-terminal glycine residues in dipeptides. We report on the application of this method to the modification of glycine residues in dipeptides, including the introduction of the functionally versatile allyl group through the free-radical reaction of brominated peptides with allyltributyltin.[6]

The dipeptides (1a - 5a) reacted with N-bromosuccinimide (1 eq.) in dichloromethane, on photolysis at reflux under nitrogen, to give the corresponding brominated peptides (1b - 5b). Although 1b - 5b were not sufficiently stable for isolation and purification, their formation was detected directly by ^{1}H n.m.r. spectroscopic analysis of crude reaction mixtures after removal of solvent. The spectra of 1b - 5b each showed a doublet resonance attributable to the α-proton of the brominated glycine residue, at δ 6.60 (J 10Hz) and 6.62 (J 10Hz) for the diastereoisomers of 1b, δ 7.04 (J 9Hz) for 2b, δ 6.95 (J 9Hz) for 3b, δ 6.90 (J 10Hz) for 4b, and δ 6.95 (J 10Hz) and 6.98 (J 10Hz) for the diastereoisomers of 5b.

Yields of the brominated peptides (1b - 5b) and the selectivity for bromination of glycine residues in 1a - 5a were gauged by preparing derivatives of 1b - 5b. The bromides (1b) and (2b) were converted to the corresponding methoxy-substituted peptides (1c) and (2c), in situ, through addition of methanol directly to crude reaction mixtures after cooling to room temperature. The peptides (1c) and (2c) were isolated in yields of 65 and 73%, based on 1a and 2a, respectively, and were fully characterised.[7,8] The bromides (2b - 5b) were reduced to the corresponding deuterated peptides (2d - 5d), in situ, through addition of tributyltin deuteride to crude reaction mixtures cooled to room temperature. The deuterated dipeptides (2d - 5d) were isolated in yields ranging from 37-54%, based on 2a - 5a, and their deuterium content was determined using mass spectrometric analysis to range



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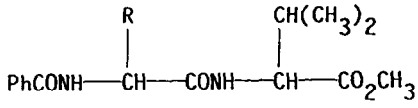

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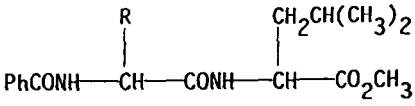

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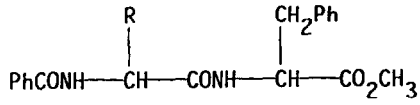

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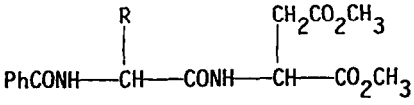

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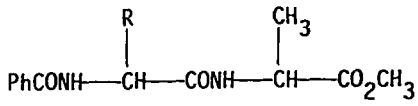

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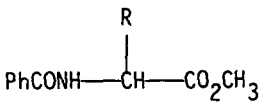

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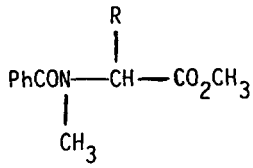

(8)

a) R=H
b) R=Br
c) R=OCH_3
d) R=D
e) R=$CH(CO_2Et)_2$
f) R=$CH_2CH{=}CH_2$

from 75-79% D_1. It was determined that the deuterium was incorporated regiospecifically at the α-position of glycine residues in **2d** - **5d**, by mass spectrometric analysis of molecular ions and ions with m/z 105 ($PhCO^{+\bullet}$), 134 ($PhCONHCH_2^{+\bullet}$) and 135 ($PhCONHCHD^{+\bullet}$).

Reaction of the glycylalanine derivative (**6a**) with N-bromosuccinimide followed by reduction with tributyltin deuteride gave **6d** in only 11% yield, regiospecifically deuterated at the α-position of the glycine residue, but with only 40% deuterium incorporation. Presumably the low yield of **6d** reflects the low selectivity in reactions of derivatives of glycine and alanine with N-bromosuccinimide.[5]

Within the scope indicated by the reactions of **1a** - **6a**, reaction of peptides with N-bromosuccinimide affords α-bromoglycine derivatives suitable for elaboration using methods previously described. Reactions of halogenated glycine derivatives with malonate anion have been utilised in syntheses of aspartic acid derivatives.[2,4] Accordingly, treatment of the brominated peptides (**1b**) and (**2b**), *in situ*, with diethyl malonate anion (2 eq.) at -10°C gave the corresponding adducts (**1e**) and (**2e**), which were fully characterised.[9,10]

Reactions of the α-bromoglycine derivative (**7b**) and the α-bromosarcosine derivative (**8b**), with allyltributyltin illustrate a complementary method for the elaboration of α-halogenated glycine derivatives. Treatment of **7b** with allyltributyltin (2 eq.), *in situ*, at room temperature gave, after chromatography on silica, the allylglycine derivative (**7f**) in 62% yield.[11] Similar treatment of the sarcosine derivative (**8b**) gave **8f** in 58% yield. The method proved suitable for the allylation of brominated glycine residues in peptides. Reaction of **1b** and **2b** afforded the corresponding allylated dipeptides (**1f**) and (**2f**), isolated in 33 and 35% yield, respectively. The allylglycine derivatives (**1f**, **2f**, **7f** and **8f**) were fully characterised.[12-15]

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References and Notes

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7. 1:1 mixture of diastereoisomers of **1c**, m.p. 127-132°C; ^{1}H n.m.r. ($CDCl_3$) δ 1.00 (d, J 8Hz, 6H), 2.15 (m, 1H), 3.34 and 3.44 (s and s, total 3H), 3.63 and 3.73 (s and s, total 3H), 4.79 (t, J 9Hz, 1H), 5.50 and 5.57 (d and d, J 9Hz and J 9Hz, total 1H) and 7.20-8.20 (m, 7H).

8. 1:1 mixture of diastereoisomers of **2c**, oil; ^{1}H n.m.r. ($CDCl_3$) δ 0.95 (d, J 7Hz, 6H), 2.20 (m, 1H), 3.53 (s, 3H), 3.97 (s, 3H), 4.60 (dd, J 5,9Hz, 1H), 5.80 and 5.90 (d and d, J 8Hz and J 8Hz, total 1H), and 7.20-8.20 (m, 7H).

9. 3:1 mixture of diastereoisomers of **1e**, m.p. 147-156°C, 18% yield based on **1a**, ^{1}H n.m.r. ($CDCl_3$) δ 1.00 (m, 6H), 1.19 (t, J 7Hz, 3H), 1.30 (t, J 7Hz, 3H), 2.25 (m, 1H), 3.73 and 3.77 (s and s, total 3H), 3.75 (m, 1H), 4.20 (m, 4H), 4.59 (t, J 8Hz, 1H), 5.36 (dd, J 4,9Hz, 1H), 6.84 (br.d, J 8Hz, 1H), 7.02 (br.d, J 9Hz, 1H) and 7.50-8.00 (m, 5H).

10. 1:1 mixture of diastereoisomers of **2e**, m.p. 119-127°C, 18% yield based on **2a**, ^{1}H n.m.r. ($CDCl_3$) δ 0.95 (m, 6H), 1.22 (t, J 7Hz, 3H), 1.33 (m, 3H), 2.17 (m, 1H), 3.66 and 3.75 (s and s, total 3H), 3.70 (m, 1H), 4.18 (m, 4H), 4.44 (m, 1H), 5.40 (m, 1H), 7.35 (br.d, J 8Hz, 1H), 7.50-7.90 (m, 5H) and 8.03 and 8.20 (br.d and br.d, J 8Hz and J 8Hz, total 1H).

11. Yields given for the allylated products (**1f**, **2f**, **7f** and **8f**) are based on the quantity of the corresponding parent glycine derivatives (**1a**, **2a**, **7a** and **8a**) used to prepare the bromides (**1b**, **2b**, **7b** and **8b**).

12. **1f**, m.p. 78-79°C; ^{1}H n.m.r. (CCl_4) δ 2.66 (m, 2H), 3.75 (s, 3H), 4.88 (m, 1H), 5.15 (m, 2H), 5.75 (m, 1H), 6.94 (br.d, J 7Hz, 1H), 7.42 (m, 3H) and 7.78 (m, 2H).

13. **2f**, oil; ^{1}H n.m.r. (CCl_4) δ 2.61 (m, 2H), 2.88 (s, 3H), 3.70 (s, 3H), 5.20 (m, 2H), 5.31 (m, 1H), 5.82 (m, 1H) and 7.50 (m, 5H).

14. 3:1 mixture of diastereoisomers of **1f**, m.p. 159-163°C; ^{1}H n.m.r. ($CDCl_3$) δ 0.95 (m, 6H), 2.20 (m, 1H), 2.55 (m, 2H), 3.70 and 3.76 (s and s, total 3H), 4.55 (m, 2H), 5.10 (m, 2H), 5.70 (m, 1H), 6.82 (br.d, J 10Hz, 1H), 7.02 (br.d, J 9Hz, 1H), and 7.40-7.90 (m, 5H).

15. 1:1 mixture of diastereoisomers of **2f**, m.p. 138-141°C; ^{1}H n.m.r. ($CDCl_3$) δ 0.93 (d, J 6Hz, 3H), 0.98 (d, J 6Hz, 3H), 2.20 (m, 1H), 2.65 (m, 2H), 3.71 and 3.76 (s and s, total 3H), 4.60 (m, 1H), 4.75 (m, 1H), 5.25 (m, 2H), 5.85 (m, 1H) and 7.10-8.10 (m, 7H).

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