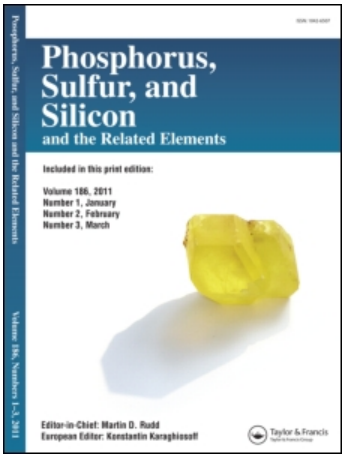

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α-Benzoyloxy- and α-Methoxy-Substituted Glycine Derivatives as Atypical Substrates for Free-Radical Reactions With Stannanes

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α-Benzoyloxy- and α-methoxy-substituted glycine derivatives undergo homolytic reactions with tributyltin hydride to give the reduction product. With allyltributyltin they afford the product of allyl group transfer and the corresponding dimeric glycine derivative, while their reactions with hexabutylditin and di-*tert*-butyl disulfide afford the dimer and the α-*tert*-butylthio-substituted glycine derivative. The free-radical nature of these reactions is most clearly demonstrated in the formation of the glycine dimer.

Keywords: benzoate; methoxide; tributyltin hydride; allyltributyltin; hexabutylditin; free-radical

INTRODUCTION

α-Bromoglycine derivatives are useful precursors for the synthesis of amino acid derivatives.[1,2] In this regard, their reactions with stannanes are illustrated by the preparation of the reduced product (**1**) through treatment of the corresponding bromide (**3**) with tributyltin hydride (FIGURE 1),[3,4] through formation of the allylglycine derivative (**5**) in the reaction of the bromide (**3**) with allyltributyltin (FIGURE 1),[4-6] and in the production of the glycine dimer (**6**) when the bromide (**3**) reacts with hexabutylditin (FIGURE 2).[7] These

reactions are typical of those displayed by organic halides on treatment with the stannanes. However, the synthetic utility of α-bromoglycine derivatives is limited by their instability. As hydrogen bromide adducts of *N*-acylimines, they decompose on storage, particularly when exposed to moisture. To circumvent this problem, we prepared the α-methoxy- and α-benzoyloxy-substituted glycine derivatives (2) and (4), by treatment of the bromide (3) with methanol and triethylamine,[8] and benzoic acid and triethylamine,[5] respectively. The ether (2) and the benzoate (4) were obtained as crystalline solids, and are stable on storage at room temperature for several months, and on distillation and chromatography. As analogues of the bromide (3), the glycine derivatives (2) and (4) are suitable for use in amino acid synthesis.[1,2] Their reactions with tributyltin hydride, allyltributyltin and hexabutylditin are presented below (FIGURES 1 and 4), and these

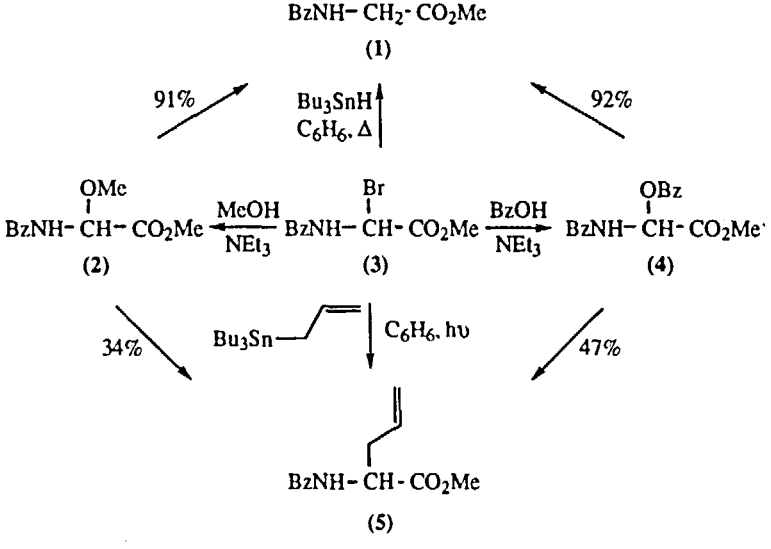


FIGURE 1. Reactions of the α-substituted glycine derivatives (2-4) with tributyltin hydride and allyltributyltin.

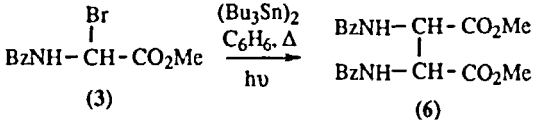


FIGURE 2. Reaction of the bromoglycine derivative (3) with hexabutylditin.

are especially noteworthy because they involve free radical reactions of stannanes with unusual substrates.

RESULTS AND DISCUSSION

Treatment of the benzoate (4) with tributyltin hydride, in benzene at reflux for 4 h, afforded a 92% yield of the reduced product (1). Using tributyltin deuteride in place of the hydride gave the corresponding α-deuterioglycine derivative, in 85% yield and with 84% deuterium incorporation. Benzoyloxytributyltin also formed in this reaction and was isolated in 27% yield. The reaction of the benzoate (4) with allyltributyltin, in refluxing benzene with photolysis to initiate the reaction, produced the allylglycine derivative (5) in 47% yield, together with a 16% yield of a 1:1 mixture of the diastereomers of the dimer (6). Similar reactions occurred when the ether (2) was treated with stannanes. The reaction with tributyltin hydride gave the glycine derivative (1), in 91% yield, while treatment with allyltributyltin produced the allylglycine derivative (5), in 34% yield, and a trace of the diastereomers of the dimer (6).

The reactions of the benzoate (4) and the ether (2) with tributyltin hydride and allyltributyltin are analogous to those of the bromide (3), and are most consistent with free radical mechanisms (FIGURE 3). It appears that tributyltin radical reacts with the glycine derivatives (2-4) by homolytic substitution to give the glycyl radical (7). This interpretation is supported by the isolation of benzoyloxytributyltin from the reaction of the benzoate (4) with tributyltin deuteride. The

glycyl radical (7) reacts by hydrogen atom abstraction from tributyltin hydride, and by allyl group transfer or dimerisation in the reactions with allyltributyltin. Production of the dimer (6) in the reaction of the bromide (3) with hexabutylditin and as a byproduct of treatment of the benzoate (4) and the ether (2) with allyltributyltin is most convincing evidence that the reactions involve free radical intermediates, as it is difficult to perceive how the dimer (6) could be formed other than by coupling of the radical (7).

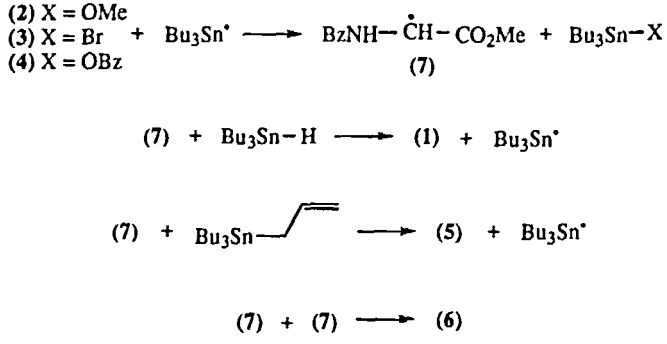


FIGURE 3. Mechanisms of reaction of the glycine derivatives (2-4) with stannanes.

The free radical nature of the reactions of the ether (2) and the benzoate (4) with stannanes is confirmed by the products resulting from their treatment with equimolar quantities of hexabutylditin and di-*tert*-butyl disulfide, under photolysis in refluxing benzene (FIGURE 4). Reaction of the benzoate (4) gave the thioether (8) and the dimer (6), in yields of 29% and 24%, respectively, while the ether (2) reacted to give the thioether (8) (19%), the dimer (6) (12%), the reduced product (1) (4%) and unreacted starting material (37%). The products of these reactions are consistent with formation of the glycyl radical (7) through homolytic displacement by tributyltin radical of the α-substituent from either the methoxide (2) or the benzoate (4). The radical (7) then reacts mainly either by homolytic substitution on the disulfide to give the thioether (8) and *tert*-butylthiyl radical or by

coupling to give the dimer (**6**). Presumably, the reduced product (**1**) forms in the reaction of the ether (**2**) by hydrogen atom transfer from either the disulfide or the stannane to the radical (**7**). Reducing the disulfide concentration resulted in a corresponding reduction in the ratio of the thioether (**8**) to the dimer (**6**), consistent with the mechanistic interpretation outlined above.

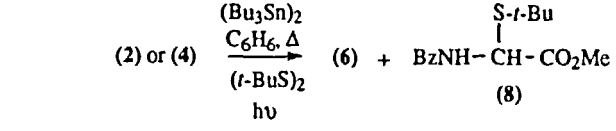
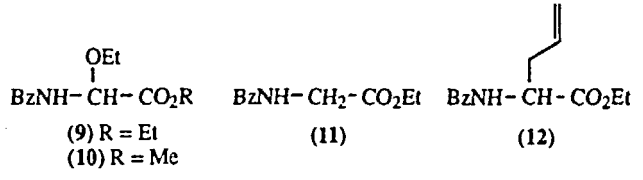


FIGURE 4. Reaction of the glycine derivatives (**2**) and (**4**) with hexabutylditin and di-*tert*-butyl disulfide.

Homolytic reduction of benzoates with tributyltin hydride has been reported twice previously, and the ease of reaction has been correlated with the stability of the intermediate substrate radicals.[9,10] This is consistent with the facile reaction of the benzoate (**4**) with stannanes, since the radical (**7**) is extensively stabilised by resonance, through the combined effects of the amido and methoxycarbonyl substituents. To the best of our knowledge, there is no literature precedent for homolytic substitution of the ether (**2**) by tributyltin radicals but the ease of this process may also be attributed to the stability of the product radical (**7**).



The ethoxyglycine derivative (**9**) reacted with tributyltin hydride and allyltributyltin to give the corresponding reduced and allyl transfer products (**11**) and (**12**). Similar reactions occurred with the

alkoxyglycine derivative (**10**) except that those reactions were complicated by competing transesterification. Nevertheless, they show that the free radical reactions of α-alkoxyglycine derivatives with stannanes are not restricted to the methoxide (**2**).

EXPERIMENTAL

General experimental details have been reported previously.[11] Photolyses were performed in quartz reaction vessels by using a Philips 300-W sunlamp. The bromide (**3**) was obtained as reported previously.[12] Tributyltin hydride, tributyltin deuteride, allyltributyltin, hexabutylditin and di-*tert*-butyl disulfide were purchased from Aldrich Chem. Co.

N-Benzoyl-α-methoxyglycine Methyl Ester (**2**)

To a solution of the bromide (**3**) (4.2 g, 15.5 mmol) in methanol (50 ml) was added triethylamine (2.4 ml, 17.3 mmol), and the mixture was stirred at room temperature for 0.25 h, then it was concentrated under reduced pressure. The residual oil was dissolved in chloroform (50ml) and the solution was washed with dilute hydrochloric acid and water, then dried and concentrated. The residue was distilled to give the title compound (**2**) as a colourless solid (2.9 g, 84%), m.p. 86-87.5° (lit.[8] 86-87°). ^{1}H NMR δ 3.55 (s, 3H, α-OMe), 3.86 (s, 3H, CO_2Me), 5.78 (d, J = 9 Hz, 1H, Hα), 7.1-7.9 (m, 6H, NH and ArH).

N-Benzoyl-α-benzoyloxyglycine Methyl Ester (**4**)

To a solution of the bromide (**3**) (1.41 g, 5.2 mmol) and benzoic acid (0.63 g, 5.2 mmol) in carbon tetrachloride (50 ml) was added triethylamine (0.72 ml, 5.2 mmol). The mixture was stirred at room temperature for 0.25 h, then it was washed with dilute hydrochloric acid (2 x 80 ml) and water (100 ml), dried and concentrated under reduced pressure. The residual oil crystallised from ethyl acetate/light petroleum to afford the title compound (**4**) as colourless needles (1.26

g, 77%), m.p. 120-122° (lit.[13] 109-110°). ^{1}H NMR δ 3.87 (s, 3H, Me), 6.84 (d, J = 9 Hz, 1H, Hα), 7.4-8.1 (m, 11H, NH and ArH). Mass spectrum *m/z* 313 (M, 0.1%), 254 (3), 122 (39), 105 (98), 77 (100), 51 (30). υ_{max} 3350, 1760, 1730, 1660 cm^{-1}.

Reaction of *N*-Benzoyl-α-methoxyglycine Methyl Ester (2) with Tributyltin Hydride

A mixture of the methoxide (2) (0.10 g, 0.45 mmol) and tributyltin hydride (0.12 ml, 0.45 mmol) in benzene (15 ml) was heated at reflux for 16 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoylglycine methyl ester (1) as a colourless solid (79 mg, 91%), m.p. 78.5-80.5° (lit.[14] 82-83°). ^{1}H NMR δ 3.70 (s, 3H, Me), 4.24 (d, J = 5 Hz, 2H, Hα), 6.9 (br, 1H, NH), 7.2-7.9 (m, 5H, ArH).

Reaction of *N*-Benzoyl-α-benzoyloxyglycine Methyl Ester (4) with Tributyltin Hydride

A mixture of the benzoate (4) (40 mg, 0.13 mmol) and tributyltin hydride (35 μl, 0.13 mmol) in benzene (4 ml) was heated at reflux for 4 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoylglycine methyl ester (1) (25 mg, 92%), identical in all respects to the sample obtained as described above.

Reaction of *N*-Benzoyl-α-benzoyloxyglycine Methyl Ester (4) with Tributyltin Deuteride

A mixture of the benzoate (4) (0.20 g, 0.64 mmol) and tributyltin deuteride (0.17 ml, 0.64 mmol) in benzene (60 ml) was heated at reflux for 4 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded benzoyloxytributyltin (70 mg, 27%), b.p. *ca.* 150°/0.05 mm (block) (Found: C, 55.1; H, 8.1. $C_{15}H_{23}O_2Sn$ requires C, 55.5; H, 7.8%). ^{1}H NMR δ 0.6-2.4 (m, 27H), 7.2-8.4 (m,

5H). Mass spectrum *m/z* 411 (M-H, 6%), 355 (100), 241 (56), 179 (82), 121 (44). Further chromatography afforded *N*-benzoyl-α-deuterioglycine methyl ester (0.11g, 85%), with physical and spectral characteristics identical to that of the non-deuterated analogue (**1**), except that the mass spectrum and the ^{1}H NMR spectrum showed 84% deuterium incorporation at the α-position.

Reaction of *N*-Benzoyl-α-methoxyglycine Methyl Ester (**2**) with Allyltributyltin

A mixture of the methoxide (**2**) (0.19 g, 0.87 mmol) and allyltributyltin (0.59 ml, 1.90 mmol) in benzene (25 ml) was irradiated at reflux for 16 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoyl-α-allylglycine methyl ester (**5**) (69 mg, 34%). Further chromatography afforded a trace of dimethyl 2,3-dibenzamidobutanedioate (**6**). The physical and spectral characteristics of the products (**5**) and (**6**) are consistent with those reported previously.[6,7]

Reaction of *N*-Benzoyl-α-benzoyloxyglycine Methyl Ester (**4**) with Allyltributyltin

A mixture of the benzoate (**4**) (0.30 g, 0.96 mmol) and allyltributyltin (0.65 ml, 2.11 mmol) in benzene (30 ml) was irradiated at reflux for 16 h, then it was concentrated under reduced pressure. The residue was triturated with light petroleum to afford a colourless solid which recrystallised from ethyl acetate/light petroleum as a 1:1 mixture of the diastereomers of dimethyl 2,3-dibenzamidobutanedioate (**6**) (30 mg, 16%). Chromatography of the mother liquor on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoyl-α-allylglycine methyl ester (**5**) (106 mg, 47%). These samples of the glycine derivatives (**5**) and (**6**) are identical in all respects to the samples obtained as described above.

Reaction of *N*-Benzoyl-α-methoxyglycine Methyl Ester (**2**) with Hexabutylditin and Di-*tert*-butyl Disulfide

A mixture of the methoxide (**2**) (0.22 g, 1.0 mmol), di-*tert*-butyldisulfide (0.19 ml, 1.0 mmol) and hexabutylditin (0.59 ml, 1.0 mmol) in benzene (30 ml) was irradiated at reflux for 14 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoyl-α-*tert*-butylthioglycine methyl ester (**8**) (51 mg, 19%), m.p. 89-91° (Found: C, 59.9; H, 6.9; N, 5.0. $C_{14}H_{19}NO_3S$ requires C, 59.8; H, 6.8; N, 5.0%). ^1H NMR δ 1.45 (s, 9H, *t*-Bu), 3.81 (s, 3H, OMe), 5.79 (d, J = 9 Hz, 1H, Hα), 6.83 (br d, J = 9 Hz, 1H, NH), 7.4-7.8 (m, 5H, ArH). Mass spectrum *m/z* 281 (M, 2%), 225 (43), 192 (29), 166 (19), 120 (9), 105 (100), 77 (86), 57 (48), 51 (33). υ_{max} 3340, 1748, 1640 cm^{-1}. Further chromatography afforded unreacted starting material (83 mg, 37%), the glycine derivative (**1**) (7 mg, 4%) and a 1:1 mixture of the diastereomers of dimethyl 2,3-dibenzamidobutanedioate (**6**) (23 mg, 12%). These samples of the glycine derivatives (**1**) and (**6**) are identical in all respects to the samples obtained as described above.

Reaction of *N*-Benzoyl-α-benzoyloxyglycine Methyl Ester (**4**) with Hexabutylditin and Di-*tert*-butyl Disulfide

A mixture of the benzoate (**4**) (0.40 g, 1.28 mmol), di-*tert*-butyldisulfide (0.25 ml, 1.28 mmol) and hexabutylditin (0.65 ml, 1.28 mmol) in benzene (25 ml) was irradiated at reflux for 14 h, then it was concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate/light petroleum, afforded *N*-benzoyl-α-*tert*-butylthioglycine methyl ester (**8**) (0.10 g, 29%) and a 1:1 mixture of the diastereomers of dimethyl 2,3-dibenzamidobutanedioate (**6**) (60 mg, 24%). These samples of the glycine derivatives (**6**) and (**8**) are identical in all respects to the samples obtained as described above.

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