N-Methylation of Carbamate Derivatives of α-Amino Acids

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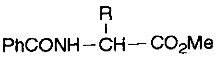
Carbamate derivatives of α-amino acids react by *N*-methylation, without racemization, on treatment with *tert*-butyl perbenzoate in the presence of copper(II) octanoate; the selective reaction of *N*-*tert*-butoxycarbonylglycine methyl ester, in preference to the corresponding alanine and valine derivatives, indicates that the relative reactivity of substrates is determined by the comparative ease of their complexation to the copper.

Copper-catalysed reactions of peresters with organic substrates are often used for introduction of the acyloxy functional group.[1] Accordingly, treatment of *N*-benzoylglycine methyl ester **1a**† with *tert*-butyl perbenzoate, in the presence of copper(II) octanoate, gave the α-benzoyloxyglycine derivative **1b**, in 67% yield. We have now found, however, that the course of reaction depends on the nature of the amino acid *N*-protecting group. With the carbamates **2a** and **2b**, the only products formed were the corresponding sarcosine derivatives **3a** and **3b**. In a typical experiment, treatment of **2a** (0.53 mmol) with *tert*-butyl perbenzoate (4.2 mmol) in the presence of copper(II) octanoate (2 mg) in benzene (40 ml) at reflux under nitrogen for 24 h, gave **3a** in 57% yield, after work-up and chromatography on silica. Under similar conditions, **2b** gave **3b** in 54% yield. Analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy showed the presence of **3a** and **3b** and the corresponding residual starting materials **2a** and **2b**, in the ratio *ca.* 3 : 1 in each case.

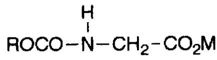
The production of **3a** and **3b** may be rationalised as shown in Scheme 1. Electron transfer from copper(I) ion to *tert*-butyl perbenzoate affords copper(II) ion, benzoate and *tert*-butoxyl radical. In turn, electron transfer from the carbamates **2a** and **2b** to copper(II) ion, followed by proton transfer, affords the corresponding carbamate radicals (presumably copper bound rather than discrete species), which react by combination with methyl radical, produced by β-scission of *tert*-butoxyl radical, to give **2b** and **3b**, respectively. The different course of reaction of **2a** and **2b**, compared to **1a**, may be attributed to the propensity of carbamates to react by electron transfer. The selective reaction of a carbamate, in preference to an amide, was clearly demonstrated in the regioselective reaction of the dipeptide derivative **4a** to give **4b**.



$\mathrm{PhCONH{-}\overset{R}{\overset{|}{C}}H{-}CO_2Me}$

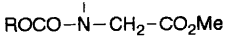
1

a; R = H
b; R = OCOPh



$\mathrm{ROCO{-}\overset{H}{\overset{|}{N}}{-}CH_2{-}CO_2Me}$

2



$\mathrm{ROCO{-}\overset{Me}{\overset{|}{N}}{-}CH_2{-}CO_2Me}$

3

a; R = Bu^t
b; R = CH$_2$Ph

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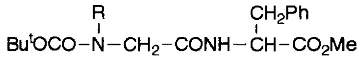
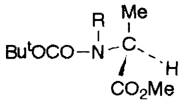
† The amino acid derivatives **1a,b**–**6a,b** used in this study, either as substrates or as authentic samples to identify products of reactions, were synthesized using standard procedures, and had spectral and physical properties consistent with those reported previously,[2–6] with the exception of **4a** and **4b** which were completely characterized as new compounds.



$Bu^tOCO\text{-}N(R)\text{-}CH_2\text{-}CONH\text{-}CH(CH_2Ph)\text{-}CO_2Me$

4



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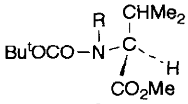


6

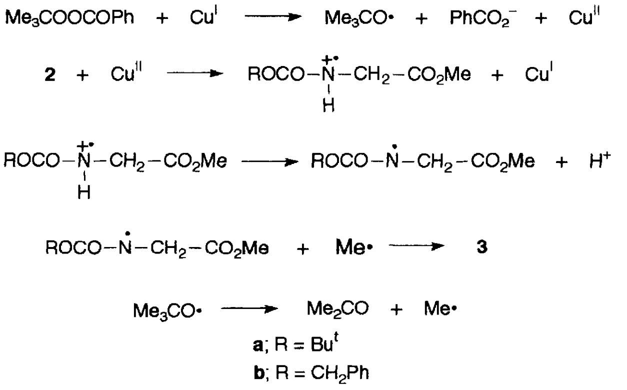
a; R = H
b; R = Me

When the (*S*)-alanine derivative **5a** was treated with *tert*-butyl perbenzoate and copper(II) octanoate, as described above, the yield of the *N*-methylamino acid derivative **5b** was 47%. Analysis of the product by ^1H NMR spectroscopy in the presence of tris[heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$],[2] and through comparison with an authentic sample of the corresponding racemate, showed that the reaction occurred without racemization.

The valine derivative **6a** was inert under the reaction conditions used to produce **3a,b**, **4b** and **5b**, from **2a,b**, **4a** and **5a**, respectively. With a mixture of the glycine derivative **2a** and the valine derivative **6a**, only the glycine derivative **2a** reacted, to give **3a**. Similarly, only the glycine derivative **2a** reacted when a mixture of **2a** and the alanine derivative **5a** was treated under the standard reaction conditions. The lack of reaction of the valine derivative **6a**, and the selective reaction of **2a** from mixtures of **2a** and **5a**, and **2a** and **6a**, may be attributed to the relative ease of complexation of these substrates to the copper catalyst. The glycine derivative **2a** binds selectively to the catalyst and, as a consequence, reacts faster than the alanine derivative **5a**. The binding of the valine derivative **6a** to copper is even less efficient, to the extent that no reaction occurs.

Earlier[7] we proposed that the preferential reaction of glycine residues in radical reactions of amino acid derivatives could be attributed to the relative stability and ease of formation of the corresponding α-carbon-centred radicals. That hypothesis does not account for the selectivity observed in the reactions of **2a**, **5a** and **6a**, nor does the rationale proposed above for the selective reaction of **2a** provide a satisfactory explanation for the selective free-radical halogenation of glycine derivatives, on which the earlier hypothesis was based. Instead, the rationale for the selective reaction of **2a** to give **2b**, by preferential binding to the copper catalyst, indicates a different factor which contributes to the selective reaction of glycine derivatives in free-radical reactions of amino acid derivatives.

In summary, the reactions of **2a**, **2b** and **4a–6a**, with *tert*-butyl perbenzoate in the presence of copper(II) octanoate, represent a novel mode of reaction of organic substrates on treatment with peresters in the presence of copper salts, they provide another aspect to account for the selective reaction of glycine residues in free-radical reactions of α-amino acid derivatives, and they illustrate a complementary[3,8] new procedure for the *N*-methylation of α-amino acid derivatives, without racemization. Studies aimed to optimize the synthetic potential of this methodology are continuing in our laboratories.



Scheme 1

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