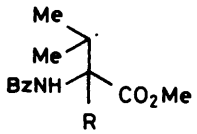
Regioselective Formation of Amidocarboxy-substituted Free Radicals

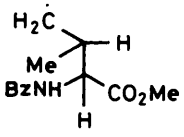
Christopher J. Easton,*[a] Michael P. Hay,[b] and Stephen G. Love[b]
[a]*Department of Organic Chemistry, University of Adelaide, G.P.O. Box 498, Adelaide, South Australia 5001*
[b]*Department of Chemistry, University of Canterbury, Christchurch 1, New Zealand*

Factors affecting the production of amidocarboxy-substituted free radicals have been investigated by examining reactions of derivatives of valine and sarcosine. Variations in the regioselectivity of reactions of these compounds are exemplified by the reactions of *N*-benzoylvaline methyl ester (**4a**) and *N*-benzoylsarcosine methyl ester (**12a**) with sulphuryl chloride and *N*-bromosuccinimide. Whereas the reaction of (**4a**) with sulphuryl chloride involves hydrogen-atom transfer from the β-position of (**4a**) with subsequent chlorine incorporation to give (**4g**), in direct contrast the reaction with *N*-bromosuccinimide proceeds *via* hydrogen-atom abstraction from the α-position of (**4a**) and yields the dibromide (**4d**). *N*-Benzoylsarcosine methyl ester (**12a**) reacts with *N*-bromosuccinimide to give the α-bromosarcosine derivative (**12b**), whereas with sulphuryl chloride the product is the *N*-chloromethylglycine derivative (**12c**). These studies indicate that amidocarboxy-substituted radicals such as (**3a**) and (**13**) are considerably more stable than the tertiary alkyl radical (**1a**) and the amido-substituted radical (**14**), respectively, but hydrogen-atom transfer reactions may afford the less stable products if electrophilic radicals are involved in the hydrogen-atom abstraction and if there is little development of radical character in the reaction transition state.

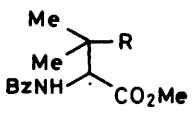
In the accompanying paper[1] we reported the regioselective chlorination of valine derivatives. Studies of the mechanism of the chlorination indicated that radicals such as (**1a**) and (**2**) are formed by direct intermolecular hydrogen-atom transfer. There was no evidence for the formation of the corresponding α-centred radical (**3a**), despite the expected greater stability of (**3a**) compared to (**1a**) and (**2**). The α-centred radical (**3a**) is stabilized



(**1**)
a; R = H
b; R = Br
c; R = Cl



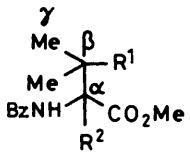
(**2**)



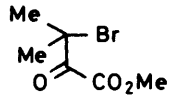
(**3**)
a; R = H
b; R = Br
c; R = Cl

by the combined action of resonance electron-donating amido and electron-withdrawing carboxy substituents.

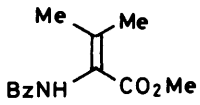
In the work described in this report[2] we have studied a variety of free-radical reactions of amino acid derivatives to investigate this anomaly.



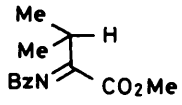
(**4**)
a; $R^1 = R^2 = H$
b; $R^1 = D, R^2 = H$
c; $R^1 = H, R^2 = D$
d; $R^1 = R^2 = Br$
e; $R^1 = R^2 = Cl$
f; $R^1 = Br, R^2 = H$
g; $R^1 = Cl, R^2 = H$



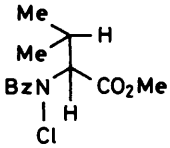
(**5**)



(**6**)



(**7**)



(**8**)

Results and Discussion

The benzoyl peroxide or photochemically initiated reaction of *N*-benzoylvaline methyl ester (**4a**) with 3 equivalents of *N*-bromosuccinimide (NBS) in carbon tetrachloride at reflux under nitrogen, afforded the dibromovaline derivative (**4d**) in high yield. Reaction with 2 equivalents of NBS gave the β-bromo-α-keto ester (**5**). Hydrogenolysis of the dibromovaline derivative (**4d**) over palladium on carbon produced a mixture of the acylenamine (**6**) and the valine derivative (**4a**). The acylenamine (**6**) was identified by comparison with an authentic sample, produced by condensation of *N*-benzoylglycine with acetone, and treatment of the product with sodium methoxide in methanol.[3] The acylenamine (**6**) was also produced by reaction of the dibromovaline derivative (**4d**) with pyridine. Treatment of (**6**) with NBS in carbon tetrachloride resulted in the formation of (**4d**).

In the reactions of (**4a**) with NBS, ^{1}H n.m.r. spectra of reaction mixtures, where less than 20% of the valine derivative (**4a**) had reacted, showed a doublet resonance at δ 1.3 p.p.m. (*J* 7 Hz) which could not be resolved further. This is consistent with formation of the acylimine (**7**) as a reaction intermediate.[4] All attempts to isolate the intermediate failed, and an attempt to synthesize an authentic sample of the acylimine (**7**) for comparison, by dehydrochlorination of the *N*-chloroamide (**8**),[4] was not successful. Trace amounts of the acylenamine (**6**) were detected in the reactions of (**4a**) with NBS, by ^{1}H n.m.r. spectroscopy and h.p.l.c. analysis.

The relative rates of reaction of (**4a**), and the deuteriated analogues (**4b**) and (**4c**), with NBS were determined using

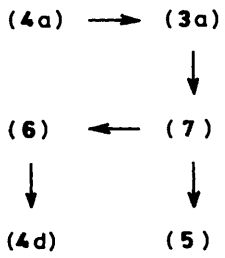
Table. Relative rates of reaction of the valine derivatives (**4a**—**c**)[a]

	Reagents		
	Sulphuryl chloride	Di-t-butyl peroxide	NBS
(**4a**)	1.0[b]	1.0[b]	1.0[b]
(**4b**)	0.80 ± 0.04	0.53 ± 0.04	1.00 ± 0.03
(**4c**)	1.00 ± 0.03	0.67 ± 0.03	0.27 ± 0.05

[a] Valine derivative and reagent in benzene under nitrogen. Reaction at reflux with irradiation by a 250-W mercury lamp. [b] Assigned as unity for each reagent.

methods described in the previous paper[1] and these are presented in the Table. Whereas the β-deuteriated valine derivative (**4b**) reacted at the same rate as the unlabelled compound (**4a**), the α-deuteriated analogue (**4c**) reacted at a reduced rate. There is a deuterium isotope effect for α-C–H bond cleavage, but no isotope effect for β-C–H bond cleavage.

Based on these results, production of (**4d**) and (**5**) in the reactions of (**4a**) with NBS can be rationalised as outlined in Scheme 1. From the deuterium isotope effect it appears that the



Scheme 1.

valine derivative (**4a**) reacts by regiospecific hydrogen-atom transfer to give the α-centred radical (**3a**). Subsequent reaction of the radical (**3a**) affords the acylimine (**7**), which hydrolyses in the presence of hydrogen bromide to give, after subsequent reaction with bromine or NBS, the β-bromo-α-keto ester (**5**). When an excess of NBS is present to remove the hydrogen bromide,[5] the acylimine (**7**) undergoes tautomerism to give the acylenamine (**6**), which reacts by the addition of bromine to give the dibromovaline derivative (**4d**).

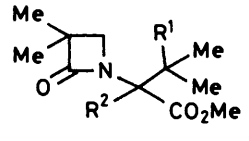
The relative rates of the photochemically induced reactions of (**4a**), and the deuteriated analogues (**4b**) and (**4c**), with di-t-butyl peroxide were measured and these are presented in Table 1, together with the relative rates of reaction of (**4a**—**c**) with sulphuryl chloride,[1] and with NBS. In direct contrast to the reactions of (**4a**—**c**) with NBS, the relative rates of reaction of (**4a**—**c**) with sulphuryl chloride exhibit a deuterium isotope effect for β-C–H bond cleavage, but no isotope effect for α-C–H bond cleavage. For reaction with di-t-butyl peroxide there is a deuterium isotope effect for both α- and β-C–H bond cleavage. It appears that whereas the reaction of (**4a**) with sulphuryl chloride involves selective hydrogen-atom transfer from the β-position to give (**1a**), the reaction with NBS proceeds *via* hydrogen-atom abstraction from the α-position of (**4a**) to give (**3a**). With di-t-butyl peroxide, reaction occurs at either position to give (**1a**) or (**3a**).

The variations in regioselectivity observed in these reactions may be interpreted in terms of the relative degrees of C–H bond homolysis in the reaction transition states.[6] With little development of radical character in the transition state of the chlorination reaction, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups acting to retard attack at the adjacent α-position by electrophilic radicals involved in the hydrogen-atom abstraction, thus favouring reaction at the β-position. The reaction with NBS is more sensitive to radical-stability effects since there is a greater degree of development of radical character in the transition state. Hydrogen-atom transfer from the α-position is favoured, therefore, because the product radical (**3a**) is stabilized by the combined effect of resonance electron-donating amido and electron-withdrawing carboxy groups. In the reaction with di-t-butyl peroxide, polar effects retarding attack at the α-position balance resonance effects facilitating reaction at that position. Thus, reaction occurs at the β-position in competition with reaction at the α-position.

In a related system we examined reactions of the dibromide (**4d**) and the corresponding dichloride (**4e**) with tributyltin hydride. The dichloride (**4e**) was obtained by treatment of the acylenamine (**6**) with sulphuryl chloride in carbon tetrachloride at room temperature. Reductions of alkyl halides by organotin hydrides proceed by halogen-atom abstraction with subsequent hydrogen incorporation. In these reactions stability of the intermediate free radical is a prime factor in determining the rate of halogen-atom abstraction.[7] In the unlikely event that halogen-atom abstraction from a vicinal dihalide affords the less stable of the possible product radicals, a facile 1,2-halogen migration to give the thermodynamically more stable radical would be expected.[8] The dihalogenated compounds (**4d**) and (**4e**) reacted with tributyltin hydride to give the corresponding β-halogenovaline derivatives (**4f**) and (**4g**). This indicates that the amidocarboxy-substituted radicals (**3b**) and (**3c**) are more stable than the corresponding β-centred radicals (**1b**) and (**1c**). Further, the production of only trace amounts of (**4a**), the product of subsequent reduction of (**4f**) and (**4g**), in the reactions with tributyltin hydride indicates that the radicals (**3b**) and (**3c**) are more stable than (**1a**).

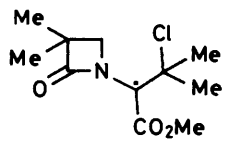
Treatment of the dichloroazetidinone (**9a**) with tributyltin hydride gave the monochloroazetidinone (**9b**), indicating that the radical (**10**) is more stable than the radical (**11a**). On this basis, production of the chlorinated azetidinone (**9b**) upon treatment of the azetidinone (**9c**) with sulphuryl chloride[1] must be attributed to polar effects, resulting in the regioselective formation of (**11b**) from (**9c**).

Reaction of *N*-benzoylsarcosine methyl ester (**12a**) with NBS afforded the α-bromosarcosine derivative (**12b**). In contrast,

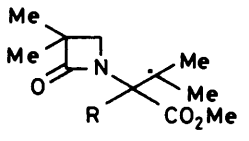


(**9**)

a ; $R^1 = R^2 = Cl$
b ; $R^1 = Cl, R^2 = H$
c ; $R^1 = R^2 = H$

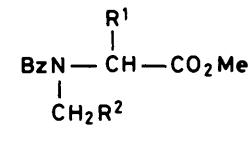


(**10**)



(**11**)

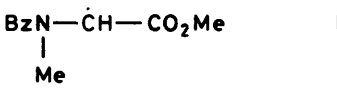
a ; R = Cl
b ; R = H



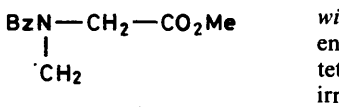
(**12**)

a ; $R^1 = R^2 = H$
b ; $R^1 = Br, R^2 = H$
c ; $R^1 = H, R^2 = Cl$

the reaction of (**12a**) with sulphuryl chloride gave the *N*-chloromethylglycine derivative (**12c**). This contrast in regioselectivity in the reactions of (**12a**) with NBS and sulphuryl chloride can also be attributed to the respective degrees of C–H bond homolysis in the transition states of the reactions. Extensive bond homolysis and development of radical character in the transition state of the reaction of (**12a**) with NBS results in reaction *via* the amidocarboxy-substituted radical (**13**), whereas the lack of development of radical character in the transition state of the reaction of (**12a**) with sulphuryl chloride is manifest in regioselectivity determined by polar effects and resulting in reaction *via* the radical (**14**).



(**13**)



(**14**)

These studies indicate that amidocarboxy-substituted radicals such as (**3a**) and (**13**) are considerably more stable than the tertiary alkyl radical (**1a**) and the amido-substituted radical (**14**), respectively, but hydrogen-atom transfer reactions may afford the less stable products if electrophilic radicals are involved in the hydrogen-atom abstraction and if there is little development of radical character in the reaction transition state.

Experimental

General experimental details have been given in the accompanying paper.[1] Methyl 2-benzamido-3-methylbut-2-enoate (**6**)[3] and *N*-benzoylsarcosine methyl ester (**12a**)[9] were prepared and purified by literature procedures.

N-*Benzoyl*-2,3-*dibromovaline Methyl Ester* (**4d**).—A mixture of *N*-benzoylvaline methyl ester (**4a**) (0.5 g, 2.1 mmol) and NBS (1.2 g, 6.7 mmol) in carbon tetrachloride (30 ml), was heated at reflux under nitrogen, while irradiated with a 250-W mercury lamp, for 0.5 h. The cooled solution was filtered and concentrated to give the title ester (**4d**) as a pale yellow oil (0.73 g, 88%); δ 2.18 (s, 6-H), 3.67 (s, 3-H), and 7.3—8.0 (m, 6-H); $\nu_{max.}$ 1 686 and 1 745 cm^{-1}; *m/z* 395, 393, and 391 (M^+, 1, 2, and 1%, respectively), 314 (10), 313 (9), 312 (10), 311 (9), and 105 (100); *m/z* 392.9387 (M^+) [Calc. for $C_{13}H_{15}Br_2NO_3$ (M^+) *m/z* 392.9400].

Methyl 3-*Bromo*-3-*methyl*-2-*oxobutanoate* (**5**).—A mixture of *N*-benzoylvaline methyl ester (**4a**) (1.0 g, 4.3 mmol) and NBS (1.6 g, 9.0 mmol) in carbon tetrachloride (20 ml), was heated at reflux under nitrogen, while irradiated with a 250-W mercury lamp, for 1 h. The cooled solution was filtered and concentrated to give an oil, which was purified by column chromatography on silica. Elution with a gradient of ethyl acetate–light petroleum gives the title ester (**5**) (0.71 g, 79%); δ ($CDCl_3$) 1.98 (s, 6-H) and 3.90 (s, 3-H); $\nu_{max.}$ 1 720 and 1 740 cm^{-1}; *m/z* 210 and 208 (M^+, 11 and 10%, respectively), 151 (49), 149 (56), 123 (100), and 121 (96); *m/z* 207.9726 (M^+) [Calc. for $C_6H_9BrO_3$ (M^+) 207.9735].

Hydrogenolysis of N-*Benzoyl*-2,3-*dibromovaline Methyl Ester* (**4d**).—A mixture of the dibromovaline derivative (**4d**) (0.2 g, 0.51 mmol), sodium acetate (0.4 g), acetic acid (0.4 g), and 5% palladium on carbon (0.1 g), in methanol–water (4:1; 10 ml), was shaken under hydrogen (1 atm) for 2 h. Celite was added, and the solution was filtered and concentrated. The residue was dissolved in ethyl acetate and the solution washed with water, dried ($MgSO_4$), and concentrated to give an oil, which was chromatographed on silica to give *N*-benzoylvaline methyl ester (**4a**) (16 mg, 13%) and methyl 2-benzamido-3-methylbut-2-enoate (**6**)[3] (47 mg, 40%).

Reaction of N-*Benzoyl*-2,3-*dibromovaline Methyl Ester* (**4d**) *with Pyridine*.—A solution of the dibromovaline derivative (**4d**) (0.2 g, 0.51 mmol) in pyridine (6 ml), was heated at reflux for 0.5 h. The cooled solution was dissolved in ethyl acetate and the solution washed with water, 0.1 M hydrochloric acid, again with water, and then dried ($MgSO_4$) and concentrated. The residue recrystallised from ethyl acetate–light petroleum to give methyl 2-benzamido-3-methylbut-2-enoate (**6**)[3] (76 mg, 64%).

Reaction of Methyl 2-*Benzamido*-3-*methylbut*-2-*enoate* (**6**) *with NBS*.—A mixture of methyl 2-benzamido-3-methylbut-2-enoate (**6**) (0.3 g, 1.3 mmol) and NBS (0.5 g, 2.8 mmol) in carbon tetrachloride (15 ml), was heated at reflux under nitrogen, while irradiated with a 250-W mercury lamp, for 0.5 h. The cooled solution was filtered and concentrated to give *N*-benzoyl-2,3-dibromovaline methyl ester (**4d**) (0.36 g, 70%), identical with a sample obtained as described above.

N-*Benzoyl*-2,3-*dichlorovaline Methyl Ester* (**4e**).—A mixture of methyl 2-benzamido-3-methylbut-2-enoate (**6**) (0.5 g, 2.1 mmol) and sulphuryl chloride (0.4 ml, 5.0 mmol) in carbon tetrachloride (50 ml), was kept at room temperature for 0.5 h and then concentrated to give the title ester (**4e**) as a pale yellow oil (0.53 g, 83%); δ 2.00 (s, 6-H), 3.66 (s, 3-H), and 7.3—8.0 (m, 6-H); $\nu_{max.}$ 1 646 and 1 742 cm^{-1}; *m/z* 303 (M^+, 1%), 270 (2), 269 (8), 268 (5), 267 (21), and 105 (100); *m/z* 267.0663 (M^+ − HCl) [Calc. for $C_{13}H_{14}ClNO_3$ (M^+ − HCl) *m/z* 267.0662].

Reaction of N-*Benzoyl*-2,3-*dibromovaline Methyl Ester* (**4d**) *with Tributyltin Hydride*.—A solution of *N*-benzoyl-2,3-dibromovaline methyl ester (**4d**) (220 mg, 0.56 mmol) and tributyltin hydride (150 mg, 0.52 mmol) in benzene (3 ml), was kept at room temperature under nitrogen for 0.5 h and then concentrated and chromatographed on silica. Elution with a gradient of ethyl acetate–light petroleum gave *N*-benzoyl-3-bromovaline methyl ester (**4f**) as a low melting solid (83 mg, 51%), m.p. 50—52 °C; δ 1.83 (s, 3-H), 2.02 (s, 3-H), 3.80 (s, 3-H), 4.78 (d, *J* 9 Hz, 1-H), 6.85 (br d, *J* 9 Hz, 1-H), and 7.2—7.8 (m, 5-H); $\nu_{max.}$ 1 650 and 1 747 cm^{-1}; *m/z* 315 and 313 (M^+, 2 and 2%, respectively), 254 (48), 256 (49), 234 (46), and 105 (100); *m/z* 315.0279 (M^+) [Calc. for $C_{13}H_{16}BrNO_3$ (M^+) *m/z* 315.0294].

Analysis of crude reaction mixtures by h.p.l.c. showed that the ratio of (**4f**) to (**4a**) produced in these reactions was greater than 100:1.

Reaction of N-*Benzoyl*-2,3-*dichlorovaline Methyl Ester* (**4e**) *with Tributyltin Hydride*.—A solution of *N*-benzoyl-2,3-dichlorovaline methyl ester (**4e**) (100 mg, 0.33 mmol) and tributyltin hydride (90 mg, 0.31 mmol) in benzene (3 ml), was kept at room temperature under nitrogen for 0.5 h and then concentrated and chromatographed on silica. Elution with a gradient of ethyl acetate–light petroleum gave *N*-benzoyl-3-chlorovaline methyl ester (**4g**) as an oil[1] (65 mg, 73%).

Analysis of crude reaction mixtures by h.p.l.c. showed that the ratio of (**4g**) and (**4a**) produced in these reactions was greater than 100:1.

N-(3-*Bromo*-2,2-*dimethylpropionyl*)*valine Methyl Ester*.—Thionyl chloride (9.4 ml, 129 mmol) was added dropwise to methanol (150 ml). Valine (7.6 g, 65 mmol) was then added and the solution was stirred at room temperature for 3 h, then concentrated to give crude valine methyl ester hydrochloride. A solution of 3-bromo-2,2-dimethylpropionic acid (7.8 g, 43 mmol) in thionyl chloride (6.3 ml, 86 mmol) was heated under reflux for 3 h and then concentrated. The residual oil was

dissolved in dichloromethane (100 ml) and the solution added dropwise to a solution of the crude valine methyl ester hydrochloride in dichloromethane (50 ml) and water (50 ml), to which potassium hydrogen carbonate was added as required to keep the solution basic. The mixture was stirred for 4 h after which the dichloromethane layer was separated, washed with water, dried ($MgSO_4$), and concentrated to give a solid which recrystallised from light petroleum to give the title ester (6.2 g, 49%), m.p. 55—56 °C; δ($CDCl_3$) 0.92 (d, *J* 6 Hz, 3-H), 0.95 (d, *J* 6 Hz, 3-H), 1.35 (s, 6-H), 2.15 (m, 1-H), 3.50 (s, 1-H), 3.53 (s, 1-H), 3.75 (s, 3-H), 4.56 (dd, *J* 4 and 8 Hz, 1-H), and 6.2 (br d, *J* 8 Hz, 1-H); $\nu_{max.}$ 1 632 and 1 750 cm^{-1} (Found: C, 45.05; H, 6.95; N, 4.67. Calc. for $C_{11}H_{20}BrNO_3$: C, 44.91; H, 6.85; N, 4.76).

1,(1-*Methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3-*dimethylazetidin*-2-*one*.—A solution of *N*-(3-bromo-2,2-dimethylpropionyl)valine methyl ester (6.1 g, 21 mmol), sulphuryl chloride (10.7 ml, 133 mmol), and benzoyl peroxide (*ca.* 100 mg), in benzene (20 ml), was heated at reflux under nitrogen for 8 h. The cooled solution was concentrated and the residue chromatographed on silica to give crude *N*-(3-bromo-2,2-dimethylpropionyl)-3-chlorovaline methyl ester as a pale yellow oil; δ($CDCl_3$) 1.42 (s, 6-H), 1.65 (s, 3-H), 1.76 (s, 3-H), 3.78 (s, 2-H), 3.81 (s, 3-H), 4.78 (d, *J* 9 Hz, 1-H), and 6.60 (br d, *J* 9 Hz, 1-H); $\nu_{max.}$ 1 638 and 1 745 cm^{-1}; *m/z* 331, 329, and 327 (M^+, 1, 6, and 8%, respectively), 165 (100) and 163 (98); *m/z* 327.0241 (M^+), [Calc. for $C_{11}H_{19}BrClNO_3$ (M^+) *m/z* 327.0236].

The oil was dissolved in a mixture of dichloromethane and dimethylformamide (4:1, 20 ml) and added dropwise to a suspension of sodium hydride (50% in oil; 1.48 g, 30.8 mmol), pre-washed with light petroleum, in a mixture of dichloromethane and dimethylformamide (4:1; 100 ml). The solution was stirred under nitrogen for 4 h and then diluted with water (10 ml). The dichloromethane layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica. Elution with a gradient of ethyl acetate–light petroleum gave the title ketone as an oil (1.7 g, 38%), b.p. 96—98 °C/16 mmHg, block; δ 1.30 (s, 6-H), 1.88 (s, 3-H), 2.17 (s, 3-H), 3.19 (s, 2-H), and 3.73 (s, 3-H); $\nu_{max.}$ 1 631, 1 720, and 1 758 cm^{-1}; *m/z* 211 (M^+, 45%), 183 (23), 180 (26), 155 (100), and 152 (64); *m/z* 211.1208 (M^+) [Calc. for $C_{11}H_{17}NO_3$ (M^+) *m/z* 211.1208].

Preparation of 1-(1,2-*Dichloro*-1-*methoxycarbonyl*-2-*methylpropyl*)-3,3-*dimethylazetidin*-2-*one* (**9a**) *and Reaction of* (**9a**) *with Tributyltin Hydride*.—A mixture of 1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3,3-dimethylazetidin-2-one (0.1 g, 0.47 mmol), and sulphuryl chloride (0.2 g, 1.5 mmol), in carbon tetrachloride (2 ml), was stirred at room temperature for 15 min and then concentrated to give the crude title ketone (**9a**) as a pale yellow oil; δ 1.24 (s, 6-H), 1.77 (s, 3-H), 1.82 (s, 3-H), 3.39 (s, 2-H), and 3.75 (s, 3-H); $\nu_{max.}$ 1 723 and 1 745 cm^{-1}; *m/z* 285, 283, and 281 (M^+, 1, 3, and 4%, respectively), 248 (3), 246 (10), and 211 (100); *m/z* 246.0891 (M^+ − Cl) [Calc. for $C_{11}H_{17}ClNO_3$ (M^+ − Cl) *m/z* 246.0897].

The oil was dissolved in benzene (2 ml) and tributyltin hydride (0.4 g, 1.4 mmol) was added. The mixture was stirred at room temperature under nitrogen for 2 h after which it was concentrated and the residue chromatographed on silica. Elution with a gradient of ethyl acetate–light petroleum gave 1-(2-chloro-1-methoxycarbonyl-2-methylpropyl)-3,3-dimethylazetidin-2-one (**9b**) as an oil [1] (38 mg, 32%).

N-*Benzoyl*-2-*bromosarcosine Methyl Ester* (**12b**).—A mixture of *N*-benzoylsarcosine methyl ester (**12a**) (0.5 g, 2.4 mmol) and NBS (0.43 g, 2.4 mmol) in carbon tetrachloride (10 ml), was heated at reflux under nitrogen, while irradiated with a 250-W mercury lamp, for 15 min. The cooled solution was filtered and concentrated to give the title ester (**12b**) as an oil (0.59 g, 86%); δ 3.12 (s, 3-H), 3.82 (s, 3-H), 6.84 (s, 1-H), and 7.3—7.6 (m, 5-H); $\nu_{max.}$ 1 662 and 1 753 cm^{-1}; *m/z* 287 and 285 (M^+, 4 and 4%, respectively), and 206 (100); *m/z* 206.0819 (M^+ − Br) [Calc. for $C_{11}H_{12}NO_3$ (M^+ − Br) *m/z* 206.0817].

N-*Benzoyl*-N-*chloromethylglycine Methyl Ester* (**12c**).—A mixture of *N*-benzoylsarcosine methyl ester (**12a**) (0.5 g, 2.4 mmol) and sulphuryl chloride (0.2 ml, 2.5 mmol) in carbon tetrachloride (10 ml), was heated at reflux under nitrogen, while irradiated with a 250-W mercury lamp, for 0.5 h. The cooled solution was filtered and concentrated to give the title ester (**12c**) as an oil (0.52 g, 89%); δ 3.78 (s, 3-H), 4.25 (s, 2-H), 5.35 (s, 2-H), and 7.3—7.7 (m, 5-H); $\nu_{max.}$ 1 659 and 1 744 cm^{-1}; *m/z* 243 and 241 (M^+, 3 and 9%, respectively), 206 (7), 205 (18), 192 (8), and 105 (100); *m/z* 205.0739 (M^+ − HCl) [Calc. for $C_{11}H_{11}NO_3$ (M^+ − HCl) *m/z* 205.0739].

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