Acyloxylation at the 4-Position of Azetidin-2-ones

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The copper-catalysed reaction of azetidin-2-ones with t-butyl perbenzoate or peracetate affords the corresponding 4-benzoyloxy- and acetoxy-substituted β-lactams, respectively. *N*-Unsubstituted 4-acyloxyazetidinones can be synthesized by dearylation of the *N*-(4-methoxyphenyl)-substituted products with ceric ammonium nitrate. Acyloxylation of β-lactams that are monosubstituted at C-3 affords predominantly *trans*-products.

4-Acetoxy- and benzoyloxy-substituted azetidin-2-ones have been used extensively in organic synthesis, particularly as precursors of β-lactam antibiotics.[1–6] Consequently, there is considerable interest in the development of methods for the synthesis of compounds of this type. Here[7] we describe a method for the synthesis of 4-acyloxy-substituted azetidinones through the copper-catalysed reaction of β-lactams with t-butyl peresters.

The only alternative procedure that has been reported for the direct acyloxylation of β-lactams at the 4-position involves the electrochemical oxidation of azetidin-2-ones in acetic acid–acetonitrile.[8] This latter method is an extension of previous work on the introduction of alkoxy substituents through electrolysis of β-lactams.[9,10] It has also been reported that oxidation of *N*-hydroxyazetidines with lead tetra-acetate gives the corresponding 1,4-diacetoxyazetidinones, but this process is thought to occur by 1,4-addition of the oxidizing agent to intermediate nitrones, not by direct substitution of β-lactams.[11]

Results and Discussion

The β-lactams (**3a**—**g**) used in this work were obtained as shown in the Scheme. The substituted propionamides (**2a**—**f**), prepared from the corresponding propionic acid derivatives (**1a**—**f**), cyclized on treatment with sodium hydride to give the corresponding β-lactams (**3a**—**f**).[12] The β-lactam (**3g**) was prepared from *N*-phthaloylserine (**1g**) *via* the amide (**2g**).[13]

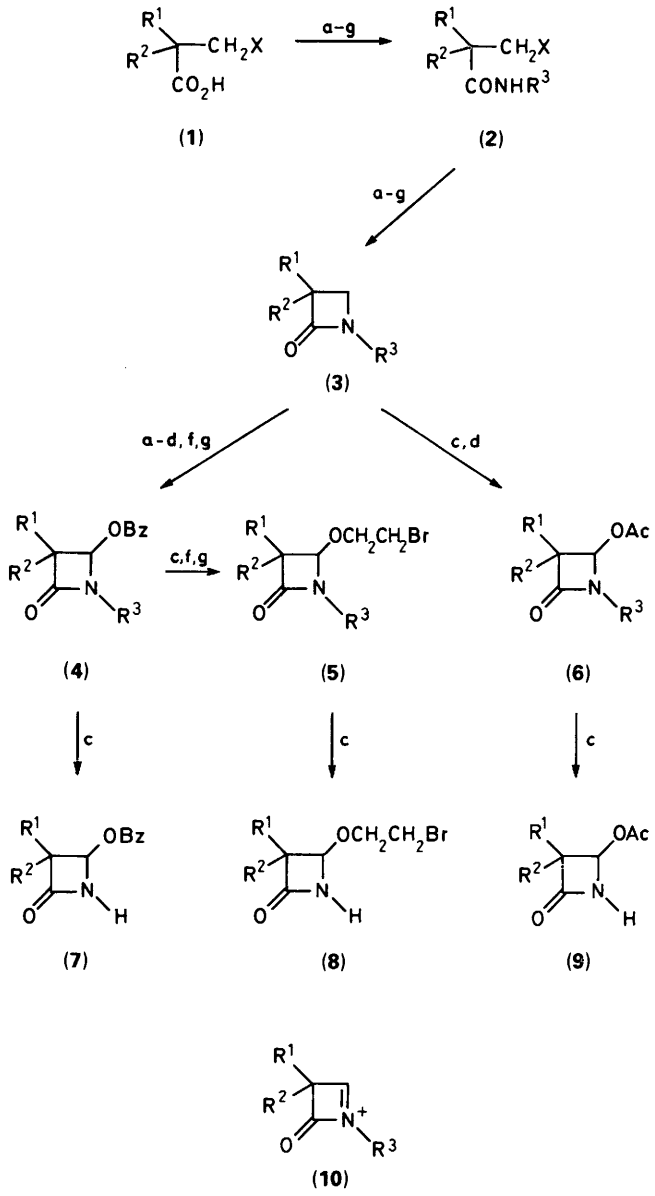
Reaction of 1-t-butylazetidin-2-one (**3a**) with t-butyl perbenzoate (*ca.* 4 equiv.) in the presence of cupric octanoate (0.025 equiv.) afforded, after chromatography of the product mixture on silica, the 4-benzoyloxy-substituted β-lactam (**4a**) in 59% yield, together with 39% unchanged (**3a**). Similar treatment of the 1-phenyl-substituted azetidinone (**3b**) gave the benzoate (**4b**) in 54% yield, with 27% unchanged (**3b**), while reaction of the 1-(*p*-methoxyphenyl)-substituted β-lactam (**3c**) afforded (**4c**) in 46% yield, together with 50% unchanged (**3c**). When larger molar excesses of t-butyl perbenzoate were used in reactions with the lactams (**3a**—**c**), lower yields of the corresponding benzoates (**4a**—**c**) were obtained. This is consistent with the observation that there was some decomposition of the benzoates (**4a**—**c**) under the reaction conditions used in their production.

The major features of the mechanism of reactions involving t-butyl perbenzoate have been elucidated.[14] Formation of (**4a**—**c**) may be attributed to hydrogen-atom transfer from the corresponding β-lactams (**3a**—**c**) to t-butoxy radical, followed by benzoate incorporation at the site of hydrogen abstraction. Clearly the methylene at the 4-position in each of the lactams (**3a**—**c**) is more reactive than the corresponding 3-methylene towards hydrogen transfer, presumably because of the activating effect of adjacent amide nitrogen.[15] For each of the lactams (**4a**—**c**), the ^{1}H n.m.r. spectrum shows unambiguously that the benzoyloxy substituent has been incorporated at the 4-position. The geminal coupling constants of 14, 16, and 16 Hz in the spectra of (**4a**—**c**), respectively, are consistent with methylene protons adjacent to the amide carbonyl group, whereas geminal coupling constants of approximately 5.5 Hz would be expected for methylene protons at the 4-position.[16]

The effect of substituents at C-3 on the reactivity of β-lactams towards reaction with t-butyl perbenzoate was investigated by studying reactions of the β-lactams (**3d**) and (**3e**). Reaction of the 3,3-dimethyl-substituted β-lactam (**3d**) afforded the corresponding benzoate (**4d**) in 44% yield. In contrast, the 3,3-diphenyl-substituted analogue (**3e**) was found to be inert under the reaction conditions, even when a twelve-fold molar excess of the perester was used. This result indicates that while the methyl substituents of the β-lactam (**3d**) do not markedly affect its reactivity, the phenyl substituents of (**3e**) reduce the reactivity of that species towards hydrogen transfer from the 4-position. As a consequence, t-butoxy radical produced by cleavage of the perbenzoate reacts by β-scission rather than by hydrogen-atom abstraction from (**3e**).

Treatment of the 3-methyl-substituted β-lactam (**3f**) with t-butyl perbenzoate afforded a mixture (*ca.* 1:3) of the *cis*- and *trans*-isomers of the corresponding benzoate (**4f**). Reaction of the 3-phthalimido-substituted lactam (**3g**) gave the *trans*-benzoate (**4g**). The stereochemistry of the benzoates (**4f**) and (**4g**) was assigned on the basis of ^{1}H n.m.r. spectral data.[16] The major isomer of (**4f**) exhibited a coupling constant of 0.9 Hz for interaction between the vicinal lactam protons, while the minor component showed a vicinal coupling constant of 4.3 Hz, consistent with the assignment of these compounds as the *trans*- and *cis*-isomers, respectively. The benzoate (**4g**) gave rise to a vicinal coupling constant of 1.3 Hz. The preferential formation of the *trans*-isomers of (**4f**) and (**4g**) may be attributed to steric interactions between the benzoyloxy group and the substituents at C-3. There is a greater selectivity for production of *trans*-(**4g**) because of the greater steric bulk of the phthalimido substituent in (**4g**) compared to the methyl substituent in (**4f**).

These reactions of the β-lactams (**3a**—**g**) with t-butyl perbenzoate illustrate a new method for the direct incorporation of a benzoyloxy substituent at the 4-position of azetidin-2-ones. The reaction products are suitable for elaboration by nucleophilic substitution of the acyloxy group. Accordingly, treatment



Scheme.

a $R^1 = R^2 = H$, $R^3 = Bu^t$, X = I
b $R^1 = R^2 = H$, $R^3 = Ph$, X = Cl
c $R^1 = R^2 = H$, R^3 = 4-MeOPh, X = Br
d $R^1 = R^2 = Me$, $R^3 = Bu^t$, X = Cl
e $R^1 = R^2 = Ph$, $R^3 = Bu^t$, X = Cl
f R^1 = Me, $R^2 = H$, R^3 = 4-MeOPh, X = Cl
g R^1 = Phth, $R^2 = H$, R^3 = 4-MeOPh, X = OH

of the benzoyloxy-substituted azetidin-2-one (**4c**) with 2-bromoethanol in the presence of zinc acetate[4] afforded the 4-(2-bromoethoxy)-substituted β-lactam (**5c**) in 57% yield. When the reaction was worked up before it had gone to completion, the acetoxy-substituted lactam (**6c**) was also isolated from the reaction mixture, indicating that the conversion of (**3c**) into (**5c**) proceeds *via* the acetate (**6c**) at least to some extent.

When the 3-methyl- and 3-phthalimido-substituted benzoyloxyazetidinones (**4f**) and (**4g**) were treated with 2-bromoethanol and zinc acetate, the corresponding bromoethoxy-substituted lactams (**5f**) and (**5g**) were produced, (**5f**) as a mixture (*ca.* 1:10) of the *cis*- and *trans*-isomers, (**5g**) as the *trans*-isomer. These results are in accord with previous studies[2,5] of nucleophilic substitution reactions of the acyloxy group in 3-substituted 4-acyloxyazetidinones, where the *trans*-product was found to predominate irrespective of the geometry of the reactant lactam. The preferential formation of the *trans*-isomers of (**5f**) and (**5g**) indicates that their production occurs *via* intermediates of type (**10f**) and (**10g**), respectively.[6]

Since substitution reactions of the 4-acyloxy group in β-lactams have been carried out more frequently with acetoxy-substituted azetidinones, in preference to their benzoyloxy-substituted analogues, we studied the incorporation of the acetoxy group in β-lactams through reaction of the azetidinones (**3c**) and (**3d**) with t-butyl peracetate. The reactions afforded the corresponding 4-acetoxy-substituted azetidinones (**6c**) and (**6d**), respectively. It should be noted, however, that t-butyl peracetate is more difficult to handle than the corresponding perbenzoate, owing to its greater thermal and shock sensitivity. Consequently, the reagent of choice for the functionalization of β-lactams is the perbenzoate. In light of the conversion of the benzoate (**4c**) into the acetate (**6c**) on treatment with zinc acetate as described above, the need for direct introduction of an acetoxy substituent is likely to be limited.

Finally, we examined reactions of the *p*-methoxyphenyl-substituted azetidinones (**4c**), (**5c**), and (**6c**) with ceric ammonium nitrate.[17] In each case cleavage of the *p*-methoxyphenyl substituent occurred, to give the corresponding *N*-unsubstituted lactams (**7c**), (**8c**), and (**9c**).

In summary, the methodology described above provides a new route for the synthesis of 4-acyloxy-substituted azetidinones that are suitable for elaboration by nucleophilic substitution of the acyloxy group, and the method can be applied to the synthesis of *N*-unsubstituted 4-acyloxyazetidinones.

Experimental

M.p.s are uncorrected. Solvents were purified and dried by standard methods. ^{1}H N.m.r. spectra were recorded on either a Varian T-60, a Varian XL-300, or a Bruker CXP-300 spectrometer. ^{13}C N.m.r. spectra were recorded on a Varian XL-300 spectrometer. Unless otherwise indicated n.m.r. spectra were recorded as dilute solutions in deuteriochloroform with tetramethylsilane as an internal standard. I.r. spectra were recorded on either a Shimadzu IR-27G or a Pye-Unicam SP3-300 spectrometer, as neat liquids or as Nujol mulls of solids. Mass spectra were recorded on either a Kratos MS-9, an AEI MS-902, or an AEI MS-3010 spectrometer. Chromatography was carried out on a Chromatotron 7924T (Harrison Research, Palo Alto/TC Research, Norwich) by using Merck silica gel 60 PF_{254}, and elution with a gradient of light petroleum–dichloromethane–ethyl acetate. Light petroleum refers to the fraction with b.p. 60—80 °C. Microanalyses were performed by the Microanalytical Laboratory, University of Otago, New Zealand, or by the Canadian Microanalytical Service Ltd., New Westminster, Canada.

t-Butyl perbenzoate, 3-chloropropionic acid (**1b**), and 3-bromopropionic acid (**1c**) were purchased from Aldrich Chemical Company, Inc. t-Butyl peracetate,[18] 3-chloro-2,2-dimethylpropionic acid (**1d**),[19] 3-chloro-2,2-diphenylpropionic acid (**1e**),[20] 3-chloro-2-methylpropionic acid (**1f**),[21] and *N*-phthaloylserine (**1g**)[22] were all prepared and purified by using literature procedures.

N-t-Butyl-3-chloropropionamide.—A mixture of the propionic acid (**1b**) (7.2 g, 67 mmol) and thionyl chloride (5.4 ml, 73 mmol) in dichloromethane (50 ml) was heated under reflux for 3 h, after which it was cooled and concentrated and the residue dissolved in dichloromethane (20 ml). t-Butylamine (11.6 ml, 110 mmol) was then added dropwise to the solution. After the mixture had been stirred at room temperature for 3 h, dichloromethane (50

ml) and water (50 ml) were added. The dichloromethane layer was separated, washed with water (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue crystallized from light petroleum–ethyl acetate to give the title propionamide (6.4 g, 58%), m.p. 78—80 °C (Found: C, 51.6; H, 8.8; N, 8.4. $C_7H_{14}ClNO$ requires C, 51.4; H, 8.6; N, 8.6%); $\nu_{max.}$ 1 568, 1 635, and 3 260 cm^{-1}; *m/z* 165 (M^+, 21%), 163 (M^+, 73), 71 (100), 65 (11), and 63 (34); δ 1.36 (s, 9 H, Bu^t), 2.53 (t, *J* 6.5 Hz, 2 H, CH_2CO), 3.76 (t, *J* 6.5 Hz, 2 H, CH_2Cl), and 5.55 (br s, 1 H, NH).

1-*t-Butylazetidin*-2-*one* (**3a**).—A mixture of *N*-t-butyl-3-chloropropionamide (2.0 g, 12.2 mmol) and sodium iodide (5.0 g, 33.3 mmol) in butan-2-one (20 ml) was heated under reflux for 3 h, after which it was cooled and diluted with ether (150 ml). The resultant solution was filtered and the filtrate was concentrated under reduced pressure. The residue separated from light petroleum to give crude *N*-t-butyl-3-iodopropionamide (**2a**) (2.0 g) as an oil which was used without further purification; δ 1.36 (s, 9 H, Bu^t), 2.68 (t, *J* 6.5 Hz, 2 H, CH_2CO), 3.35 (t, *J* 6.5 Hz, 2 H, CH_2I), and 5.25 (br s, 1 H, NH). Sodium hydride (50% in oil; 950 mg, 20 mmol) was pre-washed with light petroleum (2 × 10 ml) and suspended in a mixture of dichloromethane and dimethylformamide (4:1; 500 ml). To this suspension a solution of the crude propionamide (**2a**) (2.0 g) in dichloromethane and dimethylformamide (4:1; 200 ml) was added dropwise over 6 h, under nitrogen. The solution was stirred for a further 30 min after which saturated aqueous ammonium chloride was added. The dichloromethane layer was separated, washed with saturated brine (5 × 100 ml) and water (2 × 100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was chromatographed on silica and then distilled to give the title azetidin-2-one (**3a**) (80 mg, 5%), b.p. 77—78 °C/18 mmHg (block) (lit.,[23] 75 °C/3.5 mmHg); δ 1.36 (s, 9 H, Bu^t), 2.75 (m, 2 H, CH_2CO), and 3.17 (m, 2 H, CH_2N).

3-*Chloro*-N-*phenylpropionamide* (**2b**).—Treatment of the propionic acid (**1b**) (4.4 g, 41 mmol) with thionyl chloride (4.0 ml, 55 mmol) and then with aniline (7.7 g, 79 mmol), as described above for the preparation of *N*-t-butyl-3-chloropropionamide from the propionic acid (**1b**), thionyl chloride, and t-butylamine, afforded the title propionamide (**2b**) (6.1 g, 82%), m.p. 115—116 °C (lit.,[24] 115—116.5 °C); δ [$^2H_6$]acetone 2.86 (t, *J* 6.5 Hz, 2 H, CH_2CO), 3.90 (t, *J* 6.5 Hz, 2 H, CH_2N), and 6.80—7.80 (m, 6 H, ArH and NH).

1-*Phenylazetidin*-2-*one* (**3b**).—Treatment of the propionamide (**2b**) (1.0 g, 5.5 mmol) with sodium hydride (50% in oil; 328 mg, 6.8 mmol), as described above for the preparation of the azetidin-2-one (**3a**) from the propionamide (**2a**), gave the title azetidin-2-one (**3b**) (470 mg, 58%) as white crystals, m.p. 77—79 °C (lit.,[25] 77—78 °C); δ 3.08 (m, 2 H, CH_2CO), 3.60 (m, 2 H, CH_2N), and 7.20—7.40 (m, 5 H, ArH).

1-(4-*Methoxyphenyl*)*azetidin*-2-*one* (**3c**).—Treatment of the propionic acid (**1c**) (34.9 g, 228 mmol) with thionyl chloride (25 ml, 343 mmol) and then with 4-methoxyaniline (28 g, 228 mmol), as described above for the preparation of *N*-t-butyl-3-chloropropionamide from the propionic acid (**1b**), thionyl chloride, and t-butylamine, gave crude 3-bromo-*N*-(4-methoxyphenyl)propionamide (**2c**) (19.5 g, 33%) which was used without further purification, m.p. 132—135 °C; δ 2.94 (t, *J* 6 Hz, 2 H, CH_2CO), 3.70 (t, *J* 6 Hz, 2 H, CH_2Br), 3.80 (s, 3 H, OCH_3), and 6.70—7.50 (m, 5 H, ArH, and NH)].

Treatment of the propionamide (**2c**) (22.5 g, 87 mmol) with sodium hydride (80% in oil; 4.05 g, 135 mmol), as described above for the preparation of the azetid-1-in-2-one (**3a**) from the propionamide (**2a**), gave the title azetidin-2-one (**3c**) (8.9 g, 58%) as white crystals, m.p. 99—100 °C (lit.,[26] 97—98 °C); δ 3.05 (m, 2 H, CH_2CO), 3.60 (m, 2 H, CH_2N), 3.80 (s, 3 H, CH_3), and 6.80—7.40 (m, 4 H, ArH).

N-*t-Butyl*-3-*chloro*-2,2-*dimethylpropionamide* (**2d**).—Treatment of the propionic acid (**1d**) (9.0 g, 66 mmol) with thionyl chloride (5.4 ml, 74 mmol) and then with t-butylamine (11.6 ml, 110 mmol), as described above for the preparation of *N*-t-butyl-3-chloropropionamide from 3-chloropropionic acid (**1b**), thionyl chloride, and t-butylamine, gave the title propionamide (**2d**) (10.0 g, 79%), m.p. 78—79 °C (lit.,[27] 76.0—77.5 °C); δ(CCl_4) 1.20 (s, 6 H, 2 × CH_3), 1.32 (s, 9 H, Bu^t), 3.50 (s, 2 H, CH_2), and 5.30 (br s, 1 H, NH).

1-*t-Butyl*-3,3-*dimethylazetidin*-2-*one* (**3d**).—Treatment of the propionamide (**2d**) (1.8 g, 9.4 mmol) with sodium hydride (50% in oil; 1.1 g, 23 mmol), as described above for the preparation of the azetidin-2-one (**3a**) from the propionamide (**2a**), gave the title azetidin-2-one (**3d**) (748 mg, 51%), b.p. 60—62 °C/18 mmHg(block); *m/z* 155.1309 (M^+) [Calc for $C_9H_{17}NO$ (M^+) *m/z* 155.1310]; *m/z* 155 (M^+, 46%), 140 (12), 112 (100), 99 (38), 86 (37), 84 (37), and 70 (50); $\nu_{max.}$ 1 740 cm^{-1}; δ(CCl_4) 1.21 (s, 6 H, 2 × CH_3), 1.30 (s, 9 H, Bu^t), and 2.90 (2 H, s, CH_2).

1-*t-Butyl*-3,3-*diphenylazetidin*-2-*one* (**3e**).—Treatment of the propionic acid (**1e**) (1.8 g, 7.0 mmol) with thionyl chloride (1.0 ml, 14 mmol) and then with t-butylamine (1.9 ml, 18 mmol), as described above for the preparation of *N*-t-butyl-3-chloropropionamide from the propionic acid (**1b**), thionyl chloride, and t-butylamine, gave crude *N*-t-butyl-3-chloro-2,2-diphenylpropionamide (**2e**) (600 mg, 27%) as an oil which was used without further purification; δ 1.25 (s, 9 H, Bu^t), 4.40 (s, 2 H, CH_2Cl), 5.52 (br s, 1 H, NH), and 7.36 (s, 10 H, ArH).

Treatment of the propionamide (**2e**) (0.55 g, 1.7 mmol) with sodium hydride (50% in oil; 612 mg, 13 mmol), as described above for the preparation of the azetidin-2-one (**3a**) from the propionamide (**2a**), gave white crystals of the title azetidin-2-one (**3e**) (325 mg, 68%), m.p. 149—150 °C (Found: C, 81.9; H, 7.8; N, 4.9. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); *m/z* 280 (M^+ + 1, 1%), 236 (9), 222 (12), 180 (100), and 166 (47); $\nu_{max.}$ 1 769 cm^{-1}; δ 1.36 (s, 9 H, Bu^t), 3.68 (s, 2 H, CH_2), and 7.10—7.40 (m, 10 H, ArH).

3-*Chloro*-N-(4-*methoxyphenyl*)-2-*methylpropionamide* (**2f**).—Treatment of the propionic acid (**1f**) (28.8 g, 235 mmol) with thionyl chloride (52 ml, 713 mmol) and then with 4-methoxyaniline (19 g, 155 mmol), as described above for the preparation of *N*-t-butyl-3-chloropropionamide from the propionic acid (**1b**), thionyl chloride, and t-butylamine, gave the title propionamide (**2f**) (27.7 g, 78%), m.p. 126—127 °C (Found: C, 58.0; H, 6.2; N, 6.2. $C_{11}H_{14}ClNO_2$ requires C, 58.0; H, 6.2; N, 6.2%); *m/z* 229 (M^+, 19%), 227 (M^+, 56), and 123 (100); $\nu_{max.}$ 1 643, 1 691, and 3 420 cm^{-1}; δ 1.31 (d, *J* 7 Hz, 3 H, CCH_3), 2.70 (m, 1 H, CHCO), 3.68 (t, *J* 6 Hz, 2 H, CH_2Cl), 3.80 (s, 3 H, OCH_3), and 6.80—7.80 (m, 5 H, ArH and NH).

1-(4-*Methoxyphenyl*)-3-*methylazetidin*-2-*one* (**3f**).—Treatment of the propionamide (**2f**) (20 g, 88 mmol) with sodium hydride (80% in oil; 4.1 g, 137 mmol), as described above for the preparation of the azetidin-2-one(**3a**) from the propionamide (**2a**), gave the title azetidin-2-one (**3f**) (13.8 g, 82%) as white crystals, m.p. 117—118 °C (Found: C, 69.3; H, 6.9; N, 7.4. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.9; N, 7.3%); *m/z* 191 (M^+, 79%), 149 (70), and 135 (100); $\nu_{max.}$ 1 715 cm^{-1}; δ 1.42 (d, *J* 7 Hz, 3 H, CCH_3), 3.30 (m, 2 H, CH_2), 3.70 (m, 1 H, CH), 3.80 (s, 3 H, OCH_3), and 6.80—7.40 (m, 4 H, ArH).

N-(4-*Methoxyphenyl*)-N$^{\alpha}$-*phthaloylserinamide* (**2g**).—A mixture of *N*-phthaloylserine (13.5 g, 57 mmol), 4-methoxy-

aniline (7.8 g, 63 mmol), and dicyclohexylcarbodi-imide (27 g, 131 mmol) in dichloromethane (330 ml) was stirred at room temperature for 18 h, after which it was filtered and the supernatant dissolved in ethyl acetate (700 ml). The resulting solution was washed with 10% aqueous sodium carbonate (3 × 350 ml), 0.1M HCl (120 ml), and brine (350 ml), dried ($MgSO_4$), and concentrated. The residue crystallized from ethyl acetate to give the title serinamide (**2g**) (9.7 g, 50%), m.p. 155—156 °C (Found: C, 63.7; H, 4.9; N, 8.4. $C_{18}H_{16}N_2O_5$ requires C, 63.5; H, 4.7; N, 8.2%); *m/z* 340 (M^+, 57%), 322 (14), 150 (32), and 143 (100); $\nu_{max.}$ 1 651, 1 698, 3 250, and 3 425 cm^{-1}; δ 3.53 (t, *J* 6 Hz, 1 H, OH), 3.73 (s, 3 H, CH_3), 4.20 (m, 2 H, CH_2), 5.04 (t, *J* 6 Hz, 1 H, CH), and 6.70—8.10 (m, 9 H, ArH and NH).

1-(4-*Methoxyphenyl*)-3-*phthalimidoazetidin*-2-*one* (**3g**).—Diethyl azodicarboxylate (4.3 ml, 27 mmol) was added dropwise to a solution of the serinamide (**2g**) (8.65 g, 25 mmol) and triphenylphosphine (7.1 g, 27 mmol) in tetrahydrofuran (300 ml) under nitrogen. The mixture was stirred for 17 h at room temperature, after which the reaction was quenched with water. The resultant precipitate was collected and recrystallized from ethyl acetate to give the title azetidin-2-one (**3g**) (4.6 g, 57%) as white crystals, m.p. 232—234 °C; *m/z* 322.0971 (M^+) [Calc. for $C_{18}H_{14}N_2O_4$ (M^+) *m/z* 322.0954]; *m/z* 322 (M^+, 12%), 149 (100), and 134 (22); $\nu_{max.}$ 1 710 and 1 760 cm^{-1}; δ 3.87 (s, 3 H, CH_3), 4.07 (m, 2 H, CH_2), 5.63 (m, 1 H, CH), and 6.90—8.10 (m, 8 H, ArH).

4-*Benzoyloxy*-1-*t-butylazetidin*-2-*one* (**4a**).—A solution of the azetidin-2-one (**3a**) (80 mg, 0.63 mmol), t-butyl perbenzoate (0.44 ml, 2.3 mmol), and cupric octanoate (10 mg, 0.02 mmol) in benzene (5 ml) was heated at reflux under nitrogen for 6 h. The solution was then washed with saturated aqueous sodium metabisulphite (3 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica to give the title azetidin-2-one (**4a**) (92 mg, 59%), m.p. 94—95 °C; *m/z* 247.1212 (M^+) [Calc. for $C_{14}H_{17}NO_3$ (M^+) *m/z* 247.1208]; *m/z* 247 (M^+, 3%), 232 (15), 219 (6), 204 (8), 105 (100), and 77 (92); $\nu_{max.}$ 1 720 and 1 740 cm^{-1}, δ 1.40 (s, 9 H, Bu^t), 2.81 (dd, *J* 1, 14 Hz, 1 H, *cis*-3-H), 3.33 (dd, *J* 4, 14 Hz, 1 H, *trans*-3-H), 6.34 (dd, *J* 1, 4, Hz, 1 H, 4-H), and 7.20—8.30 (m, 5 H, ArH). Unchanged (**3a**) (31 mg, 39%) was also recovered from the reaction mixture.

4-*Benzoyloxy*-1-*phenylazetidin*-2-*one* (**4b**).—Treatment of the azetidin-2-one (**3b**) (100 mg, 0.68 mmol) with t-butyl perbenzoate (0.39 ml, 2.1 mmol), as described above for the preparation of (**4a**) gave the title azetidin-2-one (**4b**) (97 mg, 54%), m.p. 104—106 °C (Found: C, 72.2; H, 5.1; N, 4.6. $C_{16}H_{13}NO_3$ requires C, 71.9; H, 4.9; N, 5.2%); *m/z* 267.0870 (M^+) [Calc. for $C_{16}H_{13}NO_3$ (M^+) *m/z* 267.0895]; *m/z* 267 (M^+, 13%), 223 (15), 161 (42), 145 (16), 105 (100), and 77 (53); $\nu_{max.}$ 1 720 and 1 765 cm^{-1}; δ 3.17 (dd, *J* 2, 16 Hz, 1 H, *cis*-3-H), 3.66 (dd, *J* 4, 16 Hz, 1 H, *trans*-3-H), 6.74 (dd, *J* 2, 4 Hz, 1 H, 4-H), and 7.10—8.30 (m, 10 H, ArH). Unchanged (**3b**) (27 mg, 27%) was also recovered from the reaction mixture.

4-*Benzoyloxy*-1-(4-*methoxyphenyl*)*azetidin*-2-*one* (**4c**).—Treatment of the azetidin-2-one (**3c**) (1.2 g, 6.8 mmol) with t-butyl perbenzoate (7.0 ml, 37 mmol), as described above for the preparation of (**4a**), gave the title azetidin-2-one (**4c**) (0.94 g, 46%), m.p. 135—136 °C (Found: C, 68.8; H, 5.1; N, 4.7. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); *m/z* 297 (M^+, 20%), 175 (69), 149 (28), and 105 (100); $\nu_{max.}$ 1 700 and 1 740 cm^{-1}; δ 3.17 (dd, *J* 2, 16 Hz, 1 H, *cis*-3-H), 3.63 (dd, *J* 4, 16 Hz, 1 H, *trans*-3-H), 3.80 (s, 3 H, CH_3), 6.75 (dd, *J* 2, 4 Hz, 1 H, 4-H), and 6.80—8.30 (m, 9 H, ArH). Unchanged (**3c**) (0.61 g, 50%) was also recovered from the reaction mixture.

4-*Benzoyloxy*-1-*t-butyl*-3,3-*dimethylazetidin*-2-*one* (**4d**).—Treatment of the azetidin-2-one (**3d**) (100 mg, 0.65 mmol) with t-butyl perbenzoate (0.36 ml, 2 mmol), as described above for the preparation of (**4a**), gave the title azetidin-2-one (**4d**) (78 mg, 44%), m.p. 47—49 °C (Found: C, 69.7; H, 8.0; N, 4.8. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.6; N, 5.0%); *m/z* 275 (M^+, 9%), 260 (17), 176 (56), 105 (100), and 77 (73); $\nu_{max.}$ 1 720 and 1 760 cm^{-1}; δ(CCl_4) 1.10 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.39 (s, 9 H, Bu^t), 5.88 (s, 1 H, CH), and 7.30—8.20 (m, 5 H, ArH).

Treatment of 1-*t-Butyl*-3,3-*diphenylazetidin*-2-*one* (**3e**) *with t-Butyl Perbenzoate*.—When the azetidin-2-one (**3e**) (100 mg, 0.36 mmol) was treated with t-butyl perbenzoate (0.8 ml, 4.3 mmol), as described above for the preparation of (**4a**), only unchanged starting material (**3e**) (93 mg, 93%) was recovered.

trans-4-*Benzoyloxy*-1-(4-*methoxyphenyl*)-3-*methylazetidin*-2-*one* (**4f**).—Treatment of the azetidin-2-one (**3f**) (1.0 g, 5.2 mmol) with t-butyl perbenzoate (7.0 ml, 35 mmol), as described above for the preparation of (**4a**), gave the title azetidin-2-one (**4f**) (752 mg, 46%), m.p. 98—100 °C (Found: C, 69.5; H, 5.5; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%); *m/z* 311 (M^+, 4%), 189 (24), 149 (32), and 105 (100); $\nu_{max.}$ 1 720 and 1 760 cm^{-1}; δ 1.53 (d, *J* 7.5 Hz, 3 H, CCH_3), 3.40 (dq, *J* 0.9, 7.5 Hz, 1 H, 3-H), 3.78 (s, 3 H, OCH_3), 6.26 (d, *J* 0.9 Hz, 1 H, 4-H), and 6.80—8.20 (m, 9 H, ArH). Unchanged (**3f**) (287 mg, 29%) was also recovered from the reaction mixture. The ^1H n.m.r. spectrum of the crude reaction mixture showed that *cis*- and *trans*-(**4f**) were produced in the ratio *ca.* 1:3:*cis*-(**4f**), δ 1.27 (d, *J* 7.5 Hz, 3 H, CCH_3), 3.60 (m, 1 H, 3-H), 3.77 (s, 3 H, OCH_3), 6.62 (d, *J* 4.3 Hz, 1 H, 4-H), and 6.80—8.20 (m, 9 H, ArH).

trans-*Benzoyloxy*-1-(4-*methoxyphenyl*)-3-*phthalimidoazetidin*-2-*one* (**4g**).—Treatment of the azetidin-2-one (**3g**) (2.0 g, 6.2 mmol) with t-butyl perbenzoate (14 ml, 70 mmol), as described above for the preparation of (**4a**), gave the title azetidin-2-one (**4g**) (383 mg, 14%), m.p. 197—199 °C (Found: C, 67.5; H, 4.2; N, 6.1. $C_{25}H_{18}N_2O_6$ requires C, 67.9; H, 4.1; N, 6.3%); *m/z* 442 (M^+, 4%), 320 (4), 149 (15), and 105 (100); $\nu_{max.}$ 1 720, 1 780, and 1 790 cm^{-1}; δ 3.80 (s, 3 H, OCH_3), 5.55 (d, *J* 1.3 Hz, 1 H, 4-H), 6.86 (d, *J* 1.3 Hz, 1 H, 3-H), and 6.90—8.10 (m, 13 H, ArH). Unchanged (**3g**) (612 mg, 31%) was also recovered from the reaction mixture.

4-(2-*Bromoethoxy*)-1-(4-*methoxyphenyl*)*azetidin*-2-*one* (**5c**).—A mixture of the azetidin-2-one (**4c**) (3.0 g, 10 mmol), 2-bromoethanol (5.0 g, 70 mmol), and zinc acetate dihydrate (3.0 g, 13.7 mmol) in toluene (300 ml) was heated at reflux in a flask equipped with a Dean-Stark condenser for 7 h. The mixture was then cooled, washed twice with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica to give the title azetidin-2-one (**5c**) (1.73 g, 57%); *m/z* 299.0150 (M^+) [Calc. for $C_{12}H_{14}BrNO_3$ (M^+) *m/z* 299.0157]; *m/z* 301 (M^+, 8%), 299 (M^+, 8), 175 (10), 149 (100), and 134 (26); $\nu_{max.}$ 1 750 cm^{-1}; δ 3.20 (m, 2 H, 3-H), 3.50 (m, 2 H, CH_2Br), 3.83 (s, 3 H, OCH_3), 3.96 (m, 2 H, OCH_2), 5.60 (m, 1 H, 4-H), and 6.80—7.60 (m, 4 H, ArH).

When the reaction mixture was heated at reflux for <7 h, chromatography of the product mixture afforded, in addition to (**5c**), 4-acetoxy-1-(4-methoxyphenyl)azetidinone (**6c**), m.p. 100—101 °C (Found: C, 61.3; H, 5.5; N, 5.9. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N, 6.0%); *m/z* 235 (M^+, 38%), 193 (19), 175 (19), 149 (100), and 134 (40); $\nu_{max.}$ 1 750 cm^{-1}; δ 2.16 (s, 3 H, $OCOCH_3$), 3.06 (dd, *J* 2, 16 Hz, 1 H, *cis*-3-H), 3.53 (dd, *J* 4, 16 Hz, 1 H, *trans*-3-H), 3.84 (s, 3 H, OCH_3), 6.55 (dd, *J* 2, 4 Hz, 4-H), and 6.80—7.50 (m, 4 H, ArH).

trans-4-(2-*Bromoethoxy*)-1-(4-*methoxyphenyl*)-3-*methylazetidin*-2-*one* (**5f**).—Treatment of the azetidin-2-one (**4f**) (200 mg, 0.64 mmol) with 2-bromoethanol (400 mg, 5.6 mmol) and zinc acetate dihydrate (250 mg, 1.1 mmol), as described above for the preparation of the azetidin-2-one (**5c**), gave the title azetidin-2-one (**5f**) (68 mg, 33.7%), b.p. 110 °C/0.04 mmHg(block) (Found: C, 50.3; H, 5.2; N, 4.3. $C_{13}H_{16}BrNO_3$ requires C, 49.7; H, 5.1; N, 4.5%); *m/z* 315 (M^+, 32%), 313 (M^+, 32), 149 (100), and 134 (38); $\nu_{max.}$ 1 750 cm^{-1}; δ 1.38 (d, *J* 7 Hz, 3 H, CCH_3), 3.29 (dq, *J* 1.5, 7 Hz, 1 H, 3-H), 3.48 (t, *J* 6 Hz, 2 H, CH_2Br), 3.79 (s, 3 H, OCH_3), 3.91 (m, 2 H, OCH_2), 5.13 (d, *J* 1.5 Hz, 1 H, 4-H), and 6.80—7.50 (m, 4 H, ArH). The ^1H n.m.r. spectrum of the crude reaction mixture showed that *cis*- and *trans*-(**5f**) were produced in the ratio *ca.* 1:10: *cis*-(**5f**), δ 1.33 (d, *J* 7 Hz, 3 H, CCH_3), 3.40 (m, 1 H, 3-H), 3.54 (t, *J* 6 Hz, 2 H, CH_2Br), 3.79 (s, 3 H, OCH_3), 4.05 (m, 2 H, OCH_2), 5.36 (d, *J* 4 Hz, 1 H, 4-H), and 6.80—7.50 (m, 4 H, ArH).

trans-4-(2-*Bromoethoxy*)-1-(4-*methoxyphenyl*)-3-*phthalimidoazetidin*-2-*one* (**5g**).—Treatment of the azetidin-2-one (**4g**) (250 mg, 0.57 mmol) with 2-bromoethanol (800 mg, 6.4 mmol) and zinc acetate dihydrate (250 mg, 1.1 mmol), as described above for the preparation of the azetidin-2-one (**5c**), gave the title azetidin-2-one (**5g**) (92 mg, 37%) as white crystals, m.p. 58—59 °C (Found: C, 53.9; H, 3.9; N, 6.1. $C_{20}H_{17}BrN_2O_5$ requires C, 54.0; H, 3.9; N, 6.3%); *m/z* 446 (M^+, 4%), 444 (M^+, 4), 297 (42), 295 (42), 149 (100), and 134 (42); $\nu_{max.}$ 1 700 and 1 740 cm^{-1}; δ 3.50 (m, 2 H, CH_2Br), 3.80 (s, 3 H, OCH_3), 4.05 (m, 2 H, OCH_2), 5.50 (d, *J* 1.3 Hz, 1 H, 4-H), 5.80 (d, *J* 1.3 Hz, 1 H, 3-H), and 6.80—8.20 (m, 8 H, ArH).

4-*Acetoxy*-1-(4-*methoxyphenyl*)*azetidin*-2-*one* (**6c**).—Treatment of the azetidin-2-one (**3c**) (1.20 g, 6.8 mmol) with t-butyl peracetate (3.5 g, 27 mmol), as described above for the reaction of (**3c**) with t-butyl perbenzoate, gave the title azetidin-2-one (**6c**) (0.47 g, 29%), identical in all respects with the sample obtained as described above.

4-*Acetoxy*-1-*butyl*-3,3-*dimethylazetidin*-2-*one* (**6d**).—Treatment of the azetidin-2-one (**3d**) (100 mg, 0.65 mmol) with t-butyl peracetate (0.50 g, 3.8 mmol), as described above for the reaction of (**3d**) with t-butyl perbenzoate, gave the title azetidin-2-one (**6d**) (48 mg, 35%) as an oil, *m/z* 213.1371 (M^+) [Calc. for $C_{11}H_{19}NO_3$ (M^+) *m/z* 213.1365]; *m/z* 213 (M^+, 12%), 171 (38), 157 (22), and 127 (100), $\nu_{max.}$ 1 740 cm^{-1}; δ 1.11 (s, 3 H), 1.30 (s, 3 H), 1.37 (s, 9 H), 2.14 (s, 3 H), 5.75 (s, 1 H).

4-*Benzoyloxyazetidin*-2-*one* (**7c**).—To a solution of the azetidin-2-one (**4c**) (0.5 g, 1.7 mmol) in acetonitrile (20 ml) cooled to −10 °C, a solution of ceric ammonium nitrate (2.5 g, 4.6 mmol) in water (25 ml) was added dropwise. After 30 min at −10 °C, the mixture was diluted with water (110 ml) and extracted with ethyl acetate (3 × 25 ml). The organic extracts were combined, washed with 10% aqueous sodium sulphite and saturated brine, stirred over charcoal for 30 min, filtered, dried (Na_2SO_4), and concentrated. Chromatography of the residue afforded the title azetidin-2-one (**7c**) (169 mg, 53%) as colourless crystals from chloroform, m.p. 94—95 °C (lit.,[2] 93—94 °C).

4-(2-*Bromoethoxy*)*azetidin*-2-*one* (**8c**).—Treatment of the azetidin-2-one (**5c**) (140 mg, 0.41 mmol) with ceric ammonium nitrate (0.77 g, 1.4 mmol), as described above for the preparation of the azetidin-2-one (**7c**), gave the title azetidin-2-one (58 mg, 64%) as an oil, which had physical and spectral properties consistent with those reported previously.[2,8]

2-*Acetoxyazetidin*-2-*one* (**9c**).—Treatment of the azetidinone (**6c**) (200 mg, 0.85 mmol) with ceric ammonium nitrate (1.50 g, 2.7 mmol), as described above for the preparation of the azetidin-2-one (**7c**), gave the title azetidin-2-one (**9c**) (47 mg, 43%) as a low melting point solid, which had physical and spectral properties consistent with those reported previously.[2]

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