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Exocyclic Bromination of *N*-Substituted β- and γ-Lactams

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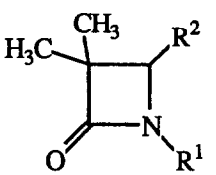
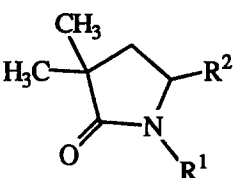
Regioselective halogenation of the *N*-susbtituted lactams (**3a**)-(**3d**) affords the corresponding exocyclic bromides (**4a**)-(**4d**). The procedure provides a novel alternative route to *N*-(α-haloalkyl)-substituted lactams, which are of particular interest in the synthesis of β-lactam antibiotics.

Reactions of *N*-substituted β- and γ-lactams at exocyclic carbon adjacent to amide nitrogen are complicated by competing reactions at the corresponding endocyclic position.[1-4] For example, the copper-catalysed reaction of (**1a**) with *t*-butyl perbenzoate afforded (**1b**) and (**1c**) as the primary products, in the ratio *ca.* 2:1,[1] while (**2a**) gave (**2b**) and (**2c**), in the ratio *ca.* 1:3.[2] Similar results were obtained through the electrochemical oxidation of lactams.[3,4] We envisaged that free-radical bromination could be affected regioselectively at the exocyclic position in lactams bearing activating substituents[5,6] at that position. Accordingly, we have investigated reactions of the azetidinones (**3a**) and (**3b**), and the pyrrolidinones (**3c**) and (**3d**), with *N*-bromosuccinimide. The lactams (**3a**)-(**3d**) used in this work were prepared by treatment of the corresponding 3-bromopropionamides and 4-chlorobutyramides with potassium hydroxide in the presence of a phase transfer catalyst.[7]



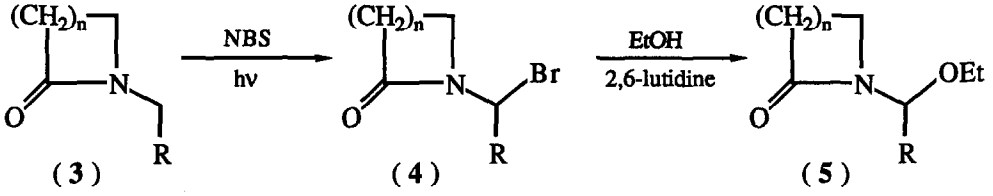
(**1**)



(**2**)

a; $R^1 = Me, R^2 = H$
b; $R^1 = CH_2OCOPh, R^2 = H$
c; $R^1 = Me, R^2 = OCOPh$

The β-lactam (**3a**) was treated with *N*-bromosuccinimide (1 equiv.) in a mixture of carbon tetrachloride and dichloromethane (5:1), at reflux under nitrogen for 0.25 hr, with reaction initiated by irradiation with a 250 W mercury lamp. The mixture was then cooled, filtered and concentrated to give only (**4a**), as determined by ^{1}H n.m.r. spectroscopic analysis [(300MHz, $CDCl_3$) δ 1.33 (3H, *t*, J 7.1 Hz), 3.01 (1H, *ddd*, J 15.6, 6.2, 3.5 Hz), 3.11 (1H, *ddd*, J 15.6, 5.9, 3.9 Hz), 3.56 (1H, *ddd*, J 6.5, 6.2, 3.9 Hz), 3.70 (1H, *ddd*, J 6.5, 5.9, 3.5 Hz), 4.27 (2H, *q*, J 7.1 Hz), 6.33 (1H, *s*)]. Similar treatment of (**3b**) gave only (**4b**) [^{1}H n.m.r. (300MHz, $CDCl_3$) δ 3.11 (1H, *ddd*, J 15.7, 6.0, 4.1 Hz), 3.21 (1H, *ddd*, J 15.7, 5.9, 4.0 Hz), 3.52 (1H, *ddd*, J 6.1, 6.0, 4.0 Hz), 3.56 (1H, *ddd*, J 6.1, 5.9, 4.1 Hz), 6.44 (1H, *s*)].



(3) (4) (5)

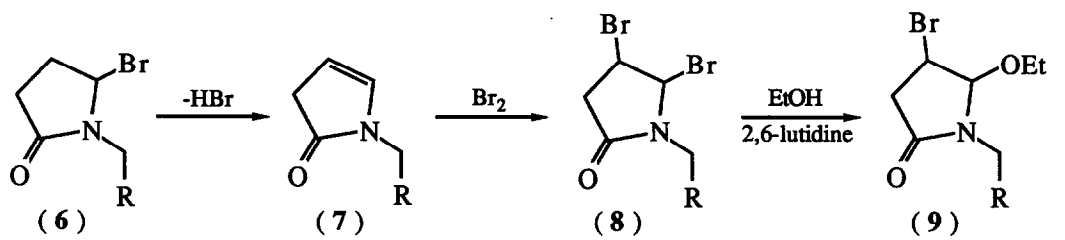
a; R = CO_2Et, n = 1
b; R = CN, n = 1
c; R = CO_2Me, n = 2
d; R = CN, n = 2

Scheme 1

Since the bromides (**4a**) and (**4b**) were not sufficiently stable for complete characterisation, they were converted to the corresponding ethers (**5a**) and (**5b**) through the addition of ethanol and 2,6-lutidine directly to crude reaction mixtures after cooling to room temperature. After purification by chromatography on silica, the ethers (**5a**) [^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.27 (3H, *t*, J 7.0 Hz), 1.32 (3H, *t*, J 7.2 Hz), 3.01 (1H, *ddd*, J 13.4, 4.9, 3.3 Hz), 3.07 (1H, *ddd*, J 13.4, 4.9, 3.9 Hz), 3.41 (1H, *ddd*, J 5.4, 4.9, 3.9 Hz), 3.46 (1H, *ddd*, J 5.4, 4.9, 3.3 Hz), 3.59 (1H, *dq*, J 9.5, 7.0 Hz), 3.68 (1H, *dq*, J 9.5, 7.0 Hz), 4.26 (2H, *q*, J 7.2 Hz), 5.35 (1H, *s*)] and (**5b**) [^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.27 (3H, *t*, J 7.0 Hz), 3.07 (1H, *ddd*, J 15.2, 5.5, 3.8 Hz), 3.13 (1H, *ddd*, J 15.2, 5.4, 3.9 Hz), 3.50 (1H, *ddd*, J 7.9, 5.5, 3.9 Hz), 3.52 (1H, *ddd*, J 7.9, 5.4, 3.8 Hz), 3.63 (1H, *dq*, J 9.3, 7.0 Hz), 3.67 (1H, *dq*, J 9.3, 7.0 Hz), 5.68 (1H, *s*)] were isolated in yields of 57 and 41%, based on (**3a**) and (**3b**), respectively, and were fully characterised. There was no evidence of ring substitution in the

reactions of (**3a**) and (**3b**) with *N*-bromosuccinimide. Presumably, the modest yields of (**5a**) and (**5b**) reflect the instability of the corresponding intermediate bromides (**4a**) and (**4b**).

Treatment of the γ-lactam (**3c**) with *N*-bromosuccinimide and subsequently with ethanol afforded, after chromatography of the reaction mixture on silica, the ether (**5c**) [37%; ^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.26 (3H, *t*, J 7.0 Hz), 2.10 (2H, *m*), 2.47 (2H, *t*, J 8.1 Hz), 3.37 (1H, *ddd*, J 9.8, 7.8, 6.5 Hz), 3.47 (1H, *ddd*, J 9.8, 7.8, 6.2 Hz), 3.57 (2H, *q*, J 7.0 Hz), 3.79 (3H, *s*), 5.75 (1H, *s*)] and the ring substitution product (**9a**) [9%; ^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.24 (3H, *t*, J 7.0 Hz), 2.76 (1H, *dd*, J 18.2, 2.9 Hz), 3.23 (1H, *ddd*, J 18.2, 7.4, 0.9 Hz), 3.61 (1H, *dq*, J 9.4, 7.0 Hz), 3.70 (1H, *dq*, J 9.4, 7.0 Hz), 3.77 (3H, *s*), 3.81 (1H, *dd*, J 17.6, 0.9 Hz), 4.24 (1H, *ddd*, J 7.4, 2.9, 1.5 Hz), 4.43 (1H, *d*, J 17.6 Hz), 5.21 (1H, *d*, J 1.5 Hz)]. Similar treatment of (**3d**) gave (**5d**) [26%; ^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.25 (3H, *t*, J 7.1 Hz), 2.15 (2H, *m*), 2.48 (2H, *t*, J 8.2 Hz), 3.60 (4H, *m*), 6.02 (1H, *s*)] and (**9b**) [8%; ^{1}H n.m.r. (300MHz, $CDCl_3$) δ 1.29 (3H, *t*, J 7.0 Hz), 2.76 (1H, *dd*, J 18.4, 2.1 Hz), 3.24 (1H, *ddd*, J 18.4, 7.2, 0.8 Hz), 3.71 (1H, *dq*, J 9.4, 7.0 Hz), 3.76 (1H, *dq*, J 9.4, 7.0 Hz), 4.07 (1H, *dd*, J 17.5, 0.8 Hz), 4.25 (1H, *ddd*, J 7.2, 2.1, 1.1 Hz), 4.51 (1H, *d*, J 17.5 Hz), 5.15 (1H, *d*, J 1.1 Hz)]. The production of (**9a**) and (**9b**) may be attributed to formation of the corresponding intermediate bromides (**6a**) and (**6b**), which react as shown in ***Scheme 2***.



(**6**) (**7**) (**8**) (**9**)

a; R = CO_2Me
b; R = CN

Scheme 2

The ratio of (**4c**) to (**8a**) in crude reaction mixtures was found to be *ca.* 3:1 as determined by ^{1}H n.m.r. spectroscopic analysis. The preferential reaction at the exocyclic position in the lactams (**3a**)-(**3d**) can be attributed to the relative ease of hydrogen atom abstraction from that position to give radicals stabilized by the combined resonance effects of the amido and alkoxycarbonyl or cyano substituents. Presumably the endocyclic methylenes adjacent to

nitrogen in the γ-lactams (**2a**), (**3c**) and (**3d**) are more reactive towards hydrogen atom abstraction than those in the corresponding β-lactams (**1a**), (**3a**) and (**3b**), due to the relative degrees of ring strain in the product radicals. Endocyclic substitution in the γ-lactams (**2a**), (**3c**) and (**3d**) is further favoured by the release of steric interactions between the C-4 and C-5 protons upon hydrogen atom abstraction from the endocyclic position.

Production of the α-bromo-2-oxoazetidineacetates (**4a**) and (**4b**) illustrates a novel attractive alternative procedure for the synthesis of *N*-(α-haloalkyl)-substituted lactams,[8] which have been used widely in the synthesis of β-lactam antibiotics.[9]

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