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DIRECT INTRODUCTION OF A BENZOYLOXY SUBSTITUENT AT THE C-4 POSITION OF β-LACTAMS

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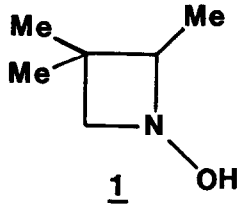
SUMMARY: The copper-promoted reaction of β-lactams with *t*-butyl perbenzoate results in benzoyloxylation of the azetidin-2-one ring at the C-4 position. There is no competing reaction at the C-3 position, but reaction at exocyclic carbon α to nitrogen competes with ring substitution.

One limit to the use of azetidinones in syntheses of β-lactam antibiotics[1] is a lack of methods for introducing a substituent directly at the C-4 position of an azetidinone ring. Oxidation of the hydroxyazetidine (1) with lead tetraacetate gave the 4-acetoxyazetidinone (2a), but this reaction is thought to occur by 1,3-addition of the oxidizing agent to the nitrone (3), not by direct substitution of the β-lactam (2b).[2] It has been



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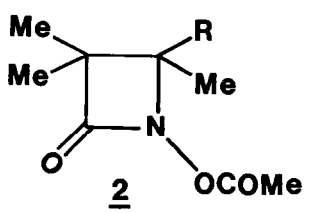

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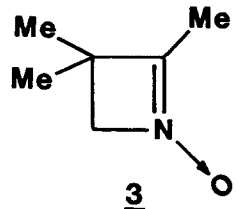
a, R=OCOMe

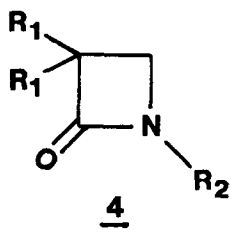
b, R=H



3

established that further substitution occurs at the azetidinone C-4 position when the site is already activated by adjacent sulphur.[3] In this communication we describe a method for functionalization of β-lactams at C-4 through the introduction of a benzoyloxy substituent. Our work is based on the knowledge that free-radical oxidation of γ- and δ-lactams occurs readily at the ring carbon α to nitrogen.[4]

The β-lactams (4a-g)[5] were prepared from corresponding 3-halopropionamides by treatment with sodium hydride.[6] To limit competing acrylamide formation in the preparations of 4a and 4b, the propionamides were added slowly, in dilute solution, to a thin suspension of sodium hydride.[7] The corresponding 3-iodopropionamide was used to prepare 4a.



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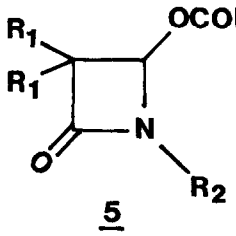

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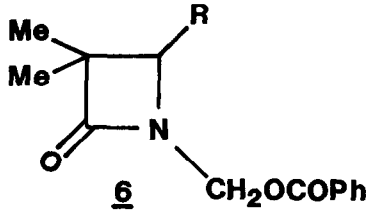
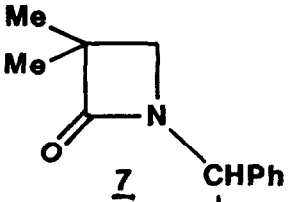
a, $R_1 = H$, $R_2 = tBu$
b, $R_1 = H$, $R_2 = Ph$
c, $R_1 = R_2 = Me$
d, $R_1 = Me$, $R_2 = CH_2Ph$
e, $R_1 = Me$, $R_2 = tBu$
f, $R_1 = Me$, $R_2 = Ph$
g, $R_1 = Ph$, $R_2 = tBu$



6

a, R = H
b, R = OCOPh



7

a, R = OH
b, R = OCOPh

Reaction of 4a (100mg, 0.8 mmol) with t-butyl perbenzoate (2.4 mmol) in the presence of cupric octanoate (0.02 mmol) in benzene (5ml) under nitrogen at reflux for 6 hr afforded, after chromatography on a Chromatotron silica gel plate, the 4-benzoyloxy substituted β-lactam (5a) [59%,[8] ^1H n.m.r. ($CDCl_3$) δ 1.40 (9H, s, tBu), 2.81 (1H, dd, J 1,14Hz, C3-Hcis), 3.33 (1H, dd, J 4,14Hz, C3-Htrans), 6.34 (1H, dd, J 1,4Hz, C4-H), and 7.2-8.3 (5H, m, Ar-H)]. Similar treatment of 4b gave 5b [53%, ^1H n.m.r. ($CDCl_3$), δ 3.17 (1H, dd, J 2,16Hz, C3-Hcis), 3.66 (1H, dd, J 4,16Hz, C3-H trans), 6.74 (1H, dd, J 2,4Hz, C4-H), and 7.1-8.3 (10H, m, Ar-H)]. The ^1H n.m.r. spectra of 5a and 5b show unambiguously that the benzoyloxy substituent has been incorporated at the C-4 position.[9] The geminal coupling constants indicate that the methylene group is adjacent to the amide carbonyl group.

The major features of the mechanism of reactions involving *t*-butyl perbenzoate have been elucidated.[10] Formation of 5a and 5b can be attributed to hydrogen-atom transfer from the corresponding β-lactams (4a) and (4b) to *t*-butoxy radical, followed by benzoate incorporation at the site of hydrogen abstraction. Clearly the C-4 methylene is more reactive than the C-3 position, presumably because of the activating effect of adjacent nitrogen.[4]

In order to examine the relative reactivity of an exocyclic carbon α to nitrogen as compared to an endocyclic carbon, the reaction of the β-lactam (4c) was investigated. The primary products of reaction of 4c with *t*-butyl perbenzoate were the endocyclic substitution product (5c) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (3H, s, CMe*cis*), 1.40 (3H, s, CMe*trans*), 2.91 (3H, s, NMe), 5.88 (1H, s, CH), and 7.3-8.3 (5H, m, Ar-H)] and the exocyclic substitution product (6a) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (6H, s, 2xCMe), 3.32 (2H, s, C-CH_2-N), 5.45 (2H, s, O-CH_2-N), and 7.3-8.3 (5H, m, Ar-H)] in the ratio *ca.*1:2. As the extent of reaction increased the disubstitution product (6b) [^{1}H n.m.r. ($CDCl_3$), δ 1.33 (3H, s, CMe*cis*), 1.45 (3H, s, CMe*trans*), 5.58 (2H, s,CH_2), 6.13 (1H, s, CH), and 7.3-8.3 (10H, m, Ar-H)] was also formed. Analysis of product ratios at varying extents of reaction showed that 6b is a secondary product formed by subsequent reaction of 5c and 6a. Formation of 5c, 6a, and 6b in the reaction of 4c demonstrates that reaction at exocyclic carbon α to nitrogen competes with ring substitution.

In the β-lactam (4f) the exocyclic carbon α to nitrogen is activated further by a phenyl substituent. The final product of reaction of 4f with *t*-butyl perbenzoate, isolated after chromatography, was the alcohol (7a) [12%, ^{1}H n.m.r. ($CDCl_3$), δ 1.26 (3H, s, Me), δ 1.33 (3H, s, Me), 2.68 (1H, d, *J* 6Hz, CH), 3.14 (1H, d, *J* 6Hz, CH), 4.30 (1H, b.s, OH), 6.36 (1H, s, CH), and 7.2-7.6 (5H, m, Ar-H)]. We attribute formation of this product to hydrolysis of the benzoate (7b) during chromatography. No ring substitution product was detected.

Finally we examined reactions of the β-lactams (4e-g) having substituents at C-3. Reactions of 4e and 4f afforded 5e [28%, ^{1}H n.m.r. (CCl_4), δ 1.10 (3H, s, Me*cis*), 1.34 (3H, s, Me*trans*), 1.39 (9H, s, *t*Bu), 5.88 (1H, s, CH), and 7.3-8.2 (5H, m, Ar-H)] and 5f [19%, ^{1}H n.m.r. ($CDCl_3$), δ 1.34 (3H, s, Me*cis*), 1.53 (3H, s, Me*trans*), 6.42 (1H, s, CH), and 7.1-8.3 (10H, m, Ar-H)], respectively. Relative yields of the benzoates (5a) and (5b) compared to (5e) and (5f) from reactions having the same molar ratio of perester indicate that substituents at C-3 reduce the reactivity. This steric effect accounts for the observation that the β-lactam (4g) was completely unreactive.

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