REACTIONS OF N-METHYL-γ-, δ-, AND ε-LACTAMS WITH t-BUTYL PERBENZOATE

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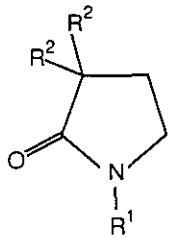
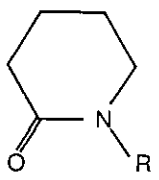
Abstract - N-Methyl-γ-, δ-, and ε-lactams reacted with t-butyl perbenzoate to give, in each case, products of oxidation at endocyclic and exocyclic carbon adjacent to amide nitrogen.

The photochemical alkylation of 2-pyrrolidinone (1a) has been reported to give products from reaction at the methylenes adjacent to the amide carbon and the amide nitrogen.[1] This is at variance with reports of the photochemical and anodic oxidation of the lactams (1a,b) and (2a,b) where the only products described were from reaction at methylene adjacent to amide nitrogen.[2-5] No products resulting from anodic or photochemical oxidation of the methyl substituent in (1b) or (2b) have been reported. In direct contrast, anodic oxidation of N-methylcaprolactam (3a) occurs regioselectively at the exocyclic carbon and no products of direct endocyclic oxidation have been reported.[4,6]



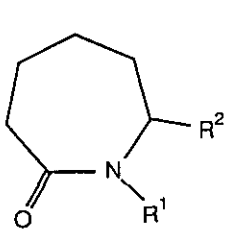
(1)

a; $R^1 = R^2 = H$
b; $R^1 = CH_3$, $R^2 = H$
c; $R^1 = R^2 = CH_3$



(2)

a; R = H
b; $R = CH_3$



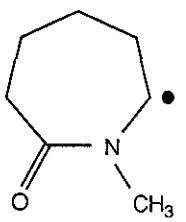
(3)

a; $R^1 = CH_3$, $R^2 = H$
b; $R^1 = CH_2OCH_3$, $R^2 = OCH_3$
c; $R^1 = CH_2OCH_3$, $R^2 = H$
d; $R^1 = CH_3$, $R^2 = OCH_3$

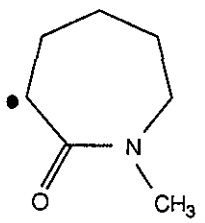
Production of the dimethoxylactam (3b) from reaction of (3a) has been attributed to subsequent endocyclic oxidation of (3c), the primary product of exocyclic oxidation, since (3c) but not (3d) was also formed in the course of the reaction.[6] The regioselectivity of anodic oxidation of N-alkylcaprolactams other than (3a) has been noted to vary from that of (3a),[7] but full details have not been reported.

Recently we reported the benzoyloxylation of β-lactams at exo- and endo-cyclic carbons adjacent to amide nitrogen.[8] The regioselectivity observed in these copper-catalysed reactions with t-butyl perbenzoate is similar to that reported for the anodic oxidation of β-lactams.[9] In view of the intriguing range of regioselectivities observed in the anodic and photochemical oxidation of the lactams (1a,b), (2a,b), and (3a), we have extended our earlier work with β-lactams to investigate reactions of the N,3,3-trimethyl-γ-lactam (1c)[10] and the N-methyl-δ- and ε-lactams (2b) and (3a)[11] with t-butyl perbenzoate. We found that pyrrolidinones without substituents at C-3 reacted to give complex intractable product mixtures.

Impetus for this work was provided by an EPR study of the reaction of N-methylcaprolactam (3a) with titanous chloride - hydrogen peroxide in a flow cell.[12] The major signal observed in the resultant spectrum indicated formation of either radical (4) or (5) [a_H (α) 22G doublet, a_H (β) 25G triplet] by hydrogen-atom transfer from (3a) to hydroxyl radical. While this experiment does not necessarily indicate the preferential formation of either (4) or (5), since other radicals may be produced and react at faster rates, it does indicate that (3a) reacts at least to some extent at endocyclic methylene adjacent to either amide nitrogen or amide carbon.

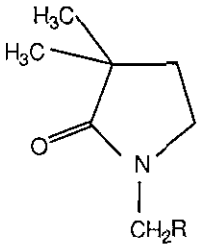


(4)



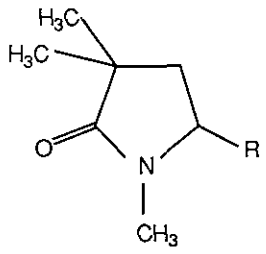
(5)

The copper-catalysed reaction of (1c) with t-butyl perbenzoate afforded, after chromatography of the reaction mixture on silica, the hydroxylactams (6a)[13,14] and (7a)[15] in yields of 16 and 17%, respectively. Analysis of crude reaction mixtures using ^{1}H nmr spectroscopy indicated that the corresponding benzoates (6b) (^{1}H nmr δ 5.61, s) and (7b) (^{1}H nmr δ 6.35, dd, J 2 and 6 Hz) were



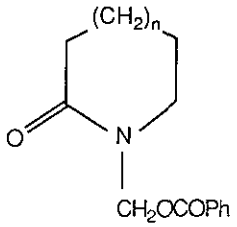
(6)

a; R = OH
b; R = OCOPh



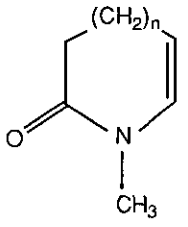
(7)

a; R = OH
b; R = OCOPh



(8)

a; n = 1
b; n = 2



(9)

a; n = 1
b; n = 2

formed in the ratio ca. 1:3, but the esters (6b) and (7b) hydrolysed to the corresponding alcohols (6a) and (7a) during chromatography. The δ-lactam (2b) reacted with t-butyl perbenzoate to give the exocyclic benzoate (8a)[16] and the olefin (9a)[17] in yields of 26 and 11%, respectively, while the ε-lactam (3a) gave (8b)[18] in 27% yield and (9b)[19] in 5% yield. Analysis of crude reaction mixtures after they were treated with triethylammonium chloride at reflux in benzene for 2 h, to facilitate elimination of any endocyclic benzoates, indicated that the δ-lactam (2b) produced (8a) and (9a) in the ratio ca. 2.3, while (8b) and (9b) were formed in the ratio ca. 3:2 by reaction of (3a).

Presumably the relatively low yields of (7a), (9a), and (9b) reflect the decomposition of these compounds during isolation. Facile reactions of (9a) and related compounds on silica have been reported.[17,20] Since (8a) was isolated in 26% yield, and (8a) and (9a) were produced in the ratio ca. 2:3, it follows that the products (8a) and (9a) reflect major reaction pathways. By similar reasoning, compounds (6a), (7a), (8b), and (9b) also reflect major reaction pathways. Thus it is clear that with each of the lactams (1c), (2b), and (3a), oxidation occurs at endocyclic and exocyclic carbon adjacent to amide nitrogen. While the major reaction of the γ- and δ-lactams (1c) and (2b) is at the endocyclic

position, with the ε-lactam (3a) and with N,3,3-trimethylazetidin-2-one[8] reaction occurs predominantly at the exocyclic carbon.

ACKNOWLEDGEMENT

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15. For (7a), ^{1}H nmr ($CDCl_3$) δ 1.08 (s, 3H), 1.20 (s, 3H), 1.76 (dd, J 3 and 14 Hz, 1H), 2.15 (dd, J 6 and 14 Hz, 1H), 2.78 (s, 3H), 5.00 (br. s, 1H) and 5.05 (dd, J 3 and 6 Hz, 1H).
16. For (8a), ^{1}H nmr ($CDCl_3$) δ 1.90 (m, 4H), 2.40 (m, 2H), 3.60 (m, 2H), 5.62 (s, 2H), 7.3-7.6 (m, 3H) and 7.9-8.3 (m, 2H).
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19. For (9b), ^{1}H nmr ($CDCl_3$) δ 1.9-2.7 (m, 6H), 3.02 (s, 3H), 5.25 (m, 1H) and 5.88 (d, J 9 Hz, 1H).
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