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Rearrangement of 3-Amido-1-hydroxyazetidin-2-ones

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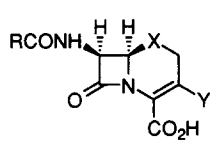
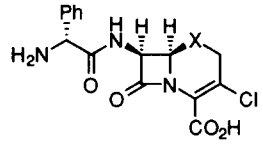
Abstract: Reactions of 3-amido-1-hydroxyazetidin-2-ones with *p*-toluenesulfonyl chloride in the presence of triethylamine or diisopropylethylamine provided 4-imidazolin-2-ones in moderate yields.

The carbacephem (**1**, X = CH_2) β-lactam antibiotics have been shown to possess broad spectrum oral activity.[1] One of these derivatives, loracarbef (**3**)[2] is well known to be a superior analog to the naturally occurring cephalosporins (**2**, X = S).[3]

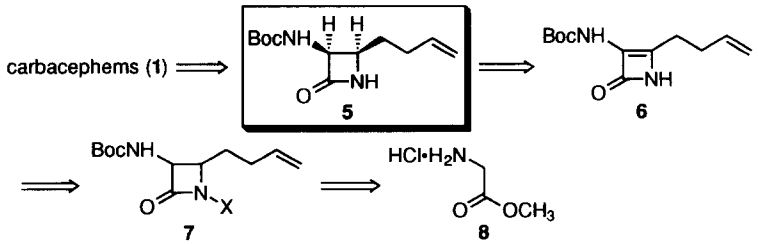


1 X = CH_2 carbacephems
2 X = S cephalosporins



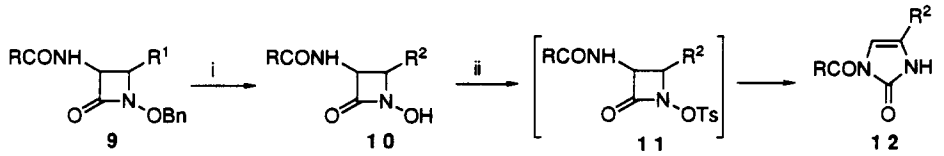
3 X = CH_2 loracarbef (Lorabid®)
4 X = S cefaclor

In a general program related to the asymmetric syntheses of carbacephem β-lactam antibiotics, we were particularly interested in developing an efficient synthesis of enantiomerically pure monocyclic β-lactams, for example compound (**5**), which could then be modified to provide bicyclic β-lactam antibiotics (Scheme 1).



Scheme 1. Retrosynthetic Plan

We anticipated that β-lactam **5** could be prepared by selective asymmetric hydrogenation of the novel unsaturated β-lactam **6**, which could be generated from tosylated β-lactam **7** (X = OTs) by elimination followed by isomerization. The β-lactam itself ultimately would be derived from glycine methyl ester **8**. During our synthesis of related tosylated β-lactams (**11**), an unusual rearrangement of 3-amido-1-hydroxyazetidin-2-ones (**10**) to 4-imidazolin-2-ones (**12**) caught our attention (Scheme 2) and is described here.



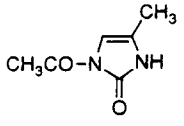
Scheme 2. i) H_2, Pd/C, MeOH; ii) TsCl, Et_3N or $(i\text{-}Pr)_2NEt$, CH_2Cl_2.

β-Lactams (**9**) were prepared according to literature procedures.[4] The benzyl group of β-lactams (**9**) was removed by catalytic hydrogenolysis in methanol in the presence of 10% Pd/C (10% w/w) to give *N*-hydroxy-β-lactams (**10**) as white solids in quantitative yields. Because of the instability of *N*-hydroxy-β-lactams,[5] they were used directly without further purification. To a solution of (**10**) in anhydrous methylene chloride was added *p*-toluenesulfonyl chloride followed by addition of triethylamine or diisopropylethylamine in order to generate *N*-(tosyloxy)-β-lactams (**11**). After 2 hours, water was added, the organic layer was separated, washed with water and brine. The organic layer was dried, filtered and evaporated. Column chromatography with EtOAc/hexanes as eluents gave 4-imidazolin-2-ones (**12**) in moderate yields. In contrast to our earlier studies of *N*-(tosyloxy)-β-lactams without amide or Boc protected amino groups at C-3,[6] we were not able to isolate any of the intermediate *N*-(tosyloxy)-β-lactams (**11**). Examples and results of the rearrangement reactions are summarized in Table 1.[7] The molecular structure of compound **12c** was also confirmed by X-ray crystallography (Figure 1).

Table 1. Rearrangement of Azetidin-2-ones (**9**) to 4-Imidazolin-2-ones (**12**)

entry	compd.	R	R^1	R^2	method[a]	prodt.	yield[b] %
1	**9a**	O^{t}Bu	$(CH_2)_2CH{=}CH_2$	n-Bu	A	**12a**	35
2	**9b**	O^{t}Bu	Me	Me	A	**12b**	55
3	**9c**	Me	Me	Me	B	**12c**	42

a. Method A: i) H_2, Pd/C, MeOH; ii) TsCl, Et_3N, CH_2Cl_2.
Method B: i) H_2, Pd/C, MeOH; ii) TsCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2.
b. Isolated yield after column chromatography.



12c

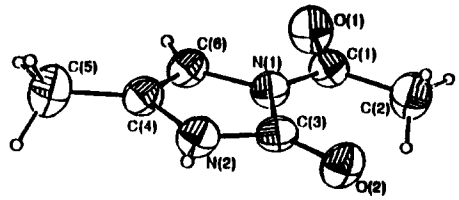
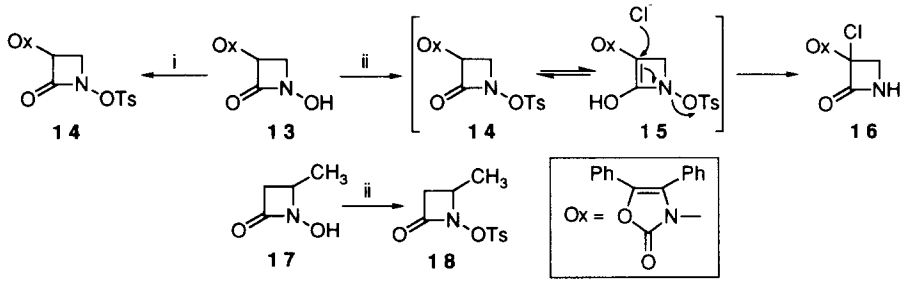


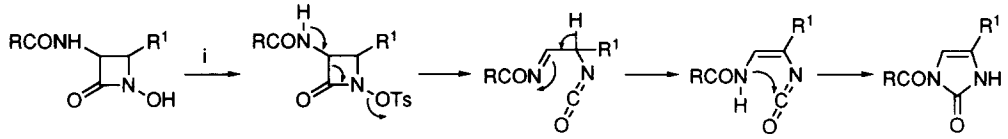
Fig. 1. X-ray structure of **12c**

Interestingly, under similar tosylation conditions, the Ox-protected β-lactam **13** in which the 3-amino group is fully protected as the oxazolinone derivative gave 3-chloro substituted β-lactam **16**. Its formation was consistent with the mechanism reported earlier,[6] which involved a nucleophilic addition of the chloride anion (Cl^-) generated in situ to the C-3 position of the β-lactam intermediate **15**. However, when β-lactam **13** was treated with toluenesulfonyl anhydride, *N*-(tosyloxy)-β-lactam **14** was obtained, but was found to be unstable to either column chromatography or recrystallization. On the other hand, when β-lactam **17** which has no substituent on the C-3 position was treated with *p*-toluenesulfonyl chloride in the presence of triethylamine, *N*-(tosyloxy)-β-lactam **18** was isolated in good yield as a white solid after column chromatography (Scheme 3).[6]



Scheme 3. i) Ts_2O, Et_3N, CH_2Cl_2; ii) TsCl, Et_3N, CH_2Cl_2.

Accordingly, the rearrangement of azetidinones to imidazolinones may utilize a pathway in which the amido side chain is involved. A proposed mechanism is described in Scheme 4. The key steps in this mechanism include a fragmentation to open the β-lactam ring followed by double bond migration and an intramolecular nucleophilic addition of the amide nitrogen to an intermediate isocyanate to give the 4-imidazolin-2-one (Scheme 4).[8]



Scheme 4. i) TsCl, Et_3N or $(i\text{-}Pr)_2NEt$, CH_2Cl_2.

Further studies on this rearrangement reaction for the synthesis of heterocyclic systems are being investigated.

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7. All new compounds gave satisfactory spectroscopic and analytical data. ^{1}H NMR spectral data for selected compounds includes: **9a** ($CDCl_3$) δ 1.42 (s, 9H), 1.56 (m, 2H), 2.03 (m, 2H), 3.60 (q, 1H, J = 6.3 Hz), 4.72 (q, 1H, J = 4.8 Hz), 4.89 (d, 1H, J = 7.7 Hz), 4.95 & 4.98 (2s, 2H), 5.02 (m, 2H), 5.70 (m, 1H), 7.40 (s, 5H). **9b** ($CDCl_3$) δ 1.25 (d, 2H, J = 5.8 Hz), 3.50 (dq, 1H, J = 0.9 & 5.6 Hz), 4.05 (d, 1H, J = 5.5 Hz), 5.10 (m, 1H), 7.40 (m, 5H). **9c** ($CDCl_3$) δ 1.28 (d, 3H, J = 6.1 Hz), 1.99 (s, 3H), 3.48-3.55 (dq, 1H, J = 1.3 & 6.2 Hz), 4.18-4.42 (dd, 1H, J = 1.6 & 5.7 Hz), 4.98 (s, 2H), 6.25 (bs, 1H), 7.37-7.42 (m, 5H). **12a** ($CDCl_3$) δ 0.92 (t, 3H, J = 7.3 Hz), 1.32-1.56 (m, 4H), 1.58 (s, 9H), 2.31-2.36 (dt, 2H, J = 1.1 & 7.6 Hz), 6.29 (t, 1H, J = 1.2 Hz), 9.84 (bs, 1H). **12b** ($CDCl_3$) δ 1.57 (s, 9H), 2.02 (d, 3H, J = 1.5 Hz), 6.31 (dq, 1H, J = 0.9 & 1.5 Hz), 9.87 (bs, 1H). **12c** ($CDCl_3$) δ 2.03 (d, 3H, J = 1.5 Hz), 2.60 (s, 3H), 6.64 (dq, 1H J = 1.0 & 1.5 Hz), 8.12 (bs, 1H). **13** (CD_3OD) δ 3.74 (t, 1H, J = 5.0 Hz), 3.96 (dd, 1H, J = 2.2 & 4.8 Hz), 4.66 (dd, 1H, J = 2.2 & 5.2 Hz), 4.88 (bs, 1H), 7.20-7.71 (m, 10H). **14** ($CDCl_3$) δ 2.46 (s, 3H), 3.91 (dd, 1H, J = 5.2 & 6.0 Hz), 4.35 (dd, 1H, J = 3.2 & 5.0 Hz), 4.62 (dd, 1H, J = 3.1 & 6.1 Hz), 7.20-7.62 (m, 12H), 7.98 (d, 2H, J = 8.4 Hz). **16** ($CDCl_3$) δ 3.82 (d, 1H, J = 7.3 Hz), 4.32 (d, 1H, J = 7.3 Hz), 6.16 (bs, 1H), 7.11-7.60 (m, 10H). **18** ($CDCl_3$) δ 1.41-1.43 (d, 3H, J = 6.1 Hz), 2.37-2.43 (dd, 1H, J = 3.1 & 14.3 Hz), 2.47 (s, 3H), 2.91-2.96 (dd, 1H, J = 6.5 & 14.3 Hz), 4.06-4.11 (m, 1H), 7.37-7.40 (d, 2H, J = 8.4 Hz), 7.87-7.90 (d, 2H, J = 8.1 Hz). ^{13}C NMR spectral data for selected compounds includes: **12a** ($CDCl_3$) δ 13.69, 22.05, 25.00, 27.95, 29.10, 83.76, 104.02, 124.27, 147.71, 152.91. **12b** ($CDCl_3$) δ 10.85, 27.93, 83.83, 104.74, 119.61, 147.52, 153.04. **12c** ($CDCl_3$) δ 10.84, 23.86, 103.66, 120.93, 153.10, 168.15. **16** ($CDCl_3$) δ 53.55, 82.19, 121.70, 124.88, 126.23, 126.73, 128.48, 129.15, 130.67, 131.90, 136.80, 152.13, 157.87. **18** ($CDCl_3$) δ 17.30, 21.41, 39.50, 55.33, 128.75, 129.71, 130.25, 146.14, 165.43.

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