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# Two-carbon ring expansion of β-lactams via N(1)–C(4) cleavage reactions

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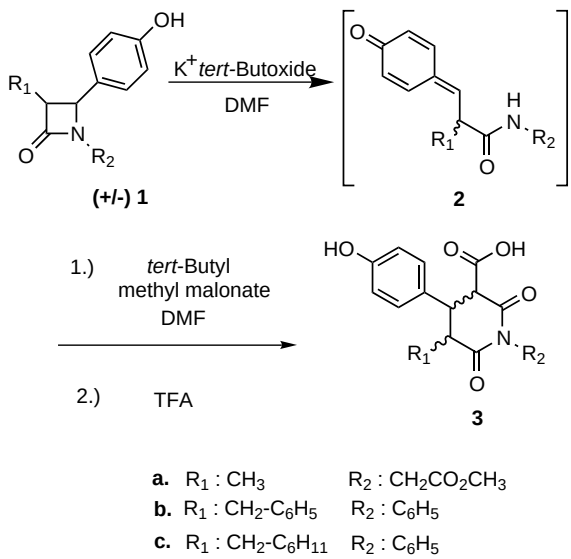
**Abstract**—The base-catalyzed ring opening of 4-(4′-hydroxyphenyl)-azetidine-2-ones with potassium *tert*-butoxide in the presence of *tert*-butyl methyl malonate gave 1,3,4,5-substituted glutarimides in a simple and efficient manner. The glutarimides were formed stereoselectively depending on the size of the 3-substituent of the β-lactam. 

Due to ring strain, β-lactams are susceptible to reactions that cleave one or more of their bonds. β-Lactam cleavage reactions have been used to expand the size of the ring to 5-membered and larger heterocycles. The weakest bond is the amide bond and amidolytic 1,2 cleavage mechanisms have been used to prepare macrocyclic alkaloids,[1] cyclic polyamines,[2] and 4-amino-3,4-dihydro-2(1*H*)-quinolones,[3] to name but a few. Scission of other bonds has also been used in mechanisms to expand the size of the ring. For example, cleavage of the C(2)–C(3) bond has been employed in the synthesis of *N*-carboxyanhydrides via Baeyer–Villiger oxidation of α-keto β-lactams.[4] Additionally, pyrazines[5] and oxazines[6] have been formed through rearrangement following C(3)–C(4) bond cleavage of substituted β-lactams.

Herein we report the first two-carbon ring expansion of a β-lactam through cleavage of the C(4)–N(1) bond. Treatment of 4-(4′-hydroxyphenyl)-azetidine-2-ones (**1**) with *tert*-butyl methyl malonate in the presence of potassium *tert*-butoxide gives the corresponding glutarimides (**3**) in good yields (Scheme 1).[7] These ring expansion reactions follow the same mechanism as our previously reported base-catalyzed 4-(4′-hydroxyphenyl) β-lactam ring opening reactions.[8] Upon potassium *tert*-butoxide addition, the phenolate anion is formed followed by rearrangement to an intermediate quinone methide (**2**), with concomitant cleavage of the C(4)–N(1) bond. The reactive quinone methide is then quenched by the *tert*-butyl methyl malonate anion in a Michael-type 1,6 conjugate addition at the benzylic carbon. Under these highly basic conditions the amide nitrogen attacks the carbonyl carbon of the methyl ester group to split off methanol and form the substituted glutarimide. The intramolecular condensation is selective for the methyl ester carbonyl carbon over that of the *tert*-butyl ester group. The *tert*-butyl group was subsequently removed with trifluoroacetic acid.




**Scheme 1.**

The stereochemistry of the ring expansion reaction is dependant on the substituent at C(3) of the starting β-lactam. In the case of methyl substitution both *trans*–

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*trans* {C(3)–C(4) and C(4)–C(5)} and *cis–trans* {C(3)–C(4) and C(4)–C(5)} stereoisomers of the glutarimide ring were present in the crude product of **3a** as judged by analysis of $^1$H NMR spectra. The ratio of stereoisomers was 2:1. In the *trans–trans* isomer, the coupling constants $J_{H3,H4}$ and $J_{H4,H5}$ were both 12 Hz indicating that the two H–C–C–H dihedral angles were approximately 180°. In the *cis–trans* isomer $J_{H3,H4}$ was 5 Hz whereas $J_{H4,H5}$ was 12 Hz. The configuration at C(5) was no doubt set by base-catalyzed epimerization to the thermodynamically more stable *trans* geometry. Thus the 1,6-conjugate addition of *tert*-butyl methyl malonate to **2a** was not stereoselective (see Table 1). In contrast, the reactions leading to **3b** and **3c** were stereospecific as only the *trans–trans* stereoisomer was present in compounds **3b–c** ($J_{H3,H4}=J_{H4,H5}=12$ Hz).

The starting β-lactams were synthesized by the [2+2] cycloaddition of ketenes derived from acid chlorides to 4-benzyloxybenzylidene amines.[9] Hydrogenolytic removal of the benzyl group gave the 4-(4′-hydroxyphenyl) starting materials. As is typical of this method, the products were racemic mixtures of *trans* β-lactams ($J_{H3,H4}=2$–3 Hz). Because of the stereospecific addition of the malonate anion, the *trans*, *trans* glutarimides, **3b** and **3c**, are racemic mixtures of enantiomers. However, because the 1,6 conjugate addition to **2a** is not stereoselective, **3a** is actually two sets of enantiomers.

Interestingly, attempts to decarboxylate the glutarimides by treatment with neat trifluoroacetic acid at either room temperature or at 60°C for 2–3 h were unsuccessful. Thus it appears that the highly constrained ring is not able to easily accommodate the change in hybridization of the C(5) atom from $sp^3$ to $sp^2$, required in the decarboxylation mechanism.

The reaction presented here has potential for the synthesis of stereochemically defined libraries of compounds that can be assayed as tyrosine mimetics. In this system, the glutarimide ring serves as a scaffold to present the phenol, to mimic the side chain of tyrosine, as well as structural diversity incorporated at N(1) and C(3) of **3**. In addition, derivatization of the carboxyl group at C(5) could also add functionality to the library. Studies on the use of this reaction in this context will be the subject of further communications.

**Table 1.** Yield and stereochemical outcome of the synthesis of **3**

| C(3) substituent | % Yield[a] | Product ratio[b] |
|---|---|---|
| **1a**, Me | 54 | 2:1 |
| **1b**, Bn | 73 | 100:0[c] |
| **1c**, $C_6H_{11}CH_2$ | 77 | 100:0[c] |

[a] Yield obtained after chromatographic purification.
[b] The ratio of *trans*/*trans* to *cis*/*trans* diastereomers. Product ratios were determined from integration of proton resonances in the $^1$H NMR spectra of crude products.
[c] Only one stereoisomer was detected.

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7. The 4-(4′-hydroxyphenyl)-azetidine-2-one (1.0 equiv.) was combined with *tert*-butyl methyl malonate (2.0 equiv.) in dry DMF and cooled to 0°C followed by dropwise addition of 2.0 equiv. of potassium *tert*-butoxide (1 M in THF). After 1/2 h the reaction solution was warmed to room temperature. The reactions were typically complete within 30 h. The butoxycarbonyl group was converted to the carboxylic acid in neat TFA at room temperature for 2 h. **3a** (mixed isomers) mp 174.1–174.5°C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.22 (m, 2H), 6.83 (d, $J=8$ Hz, 2H), 4.53 (m, 2H), 4.18 (d, $J=12$ Hz, 1H), 3.87–3.31 {3.87 (d, $J=5$ Hz, 0.37/1H), 3.31 (t, $J=12$ Hz, 0.65/1H)}, 3.71–3.70 {3.71 (s, 1.87/3H), 3.70 (s, 1.05/3H)}, 3.10 (m, 1H), 1.11–1.05 {1.11 (d, $J=8$ Hz, 1.1/3H), 1.05 (d, $J=8$ Hz, 1.9/3H), $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 174.32, 173.78, 169.15, 168.93, 168.77, 168.43, 157.12, 130.01, 129.59, 129.40, 128.98, 115.85, 56.98, 51.95, 45.16, 42.27, 42.14, 41.22, 41.13, 40.45, 13.58, 12.30. Anal. calcd C, 57.31; H, 5.11; N, 4.18. Found: C, 57.21; H, 5.24; N, 3.80%.
**3b**, mp 201.9–202.2°C; $^1$H NMR (500 MHz, acetone-$d_6$): $\delta$ 9.46 (b, 1H), 7.48 (t, $J=7$ Hz, 2H), 7.41 (t, $J=7$ Hz, 1H), 7.24 (t, $J=8$ Hz, 2H), 7.17 (d, $J=8$ Hz, 3H), 7.10 (d, $J=7$ Hz, 2H), 6.96 (d, $J=7$ Hz, 2H), 6.80 (d, $J=8$ Hz, 2H), 4.27 (d, $J=12$ Hz, 1H), 3.60 (m, 1H), 3.40 (t, $J=12$ Hz, 1H), 2.98 (d, $J=14$ Hz, 1H), 2.70 (dd, $J=14$ Hz, $2J=7$ Hz, 1H), $^{13}$C NMR (125 MHz, DMSO): $\delta$ 174.52, 169.99, 169.88, 157.56, 140.04, 136.68, 130.20, 130.00, 129.86, 129.80, 129.48, 129.07, 128.96, 126.96, 116.35, 57.84, 48.92, 42.45, 34.01. Anal. calcd C, 72.28; H, 5.10; N, 3.37. Found: C, 71.06; H, 5.16; N, 3.06%.
**3c**, mp 215.5–215.7°C; $^1$H NMR (500 MHz, acetone-$d_6$): $\delta$ 7.46 (t, $J=8$ Hz, 2H), 7.39 (t, $J=7$ Hz, 1H), 7.15 (t, $J=8$ Hz, 4H), 6.75 (d, $J=8$ Hz, 2H), 4.25 (d, $J=12$ Hz, 1H), 3.40 (t, $J=12$ Hz, 1H), 3.17 (m, 1H),1.53 (m, 6H), 1.28 (b,

1H), 1.07 (m, 4H), 0.67 (m, 1H), 0.42 (m, 1H). $^{13}$C NMR (125 MHz, DMSO): $\delta$ 175.42, 170.24, 170.05, 157.33, 136.84, 130.29, 129.99, 129.75, 129.56, 128.94, 116.12, 57.88, 44.67, 43.79, 36.55, 36.174, 34.41, 32.63, 26.83, 26.60, 26.41. Anal. calcd C, 71.24; H, 6.46; N, 3.32. Found: C, 68.50; H, 6.24; N, 2.84%.

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