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The synthesis of 'tyrosyl' peptidomimetics by acid-catalyzed N(1)–C(4) ring opening of 4-(4′-hydroxyphenyl)-azetidine-2-ones

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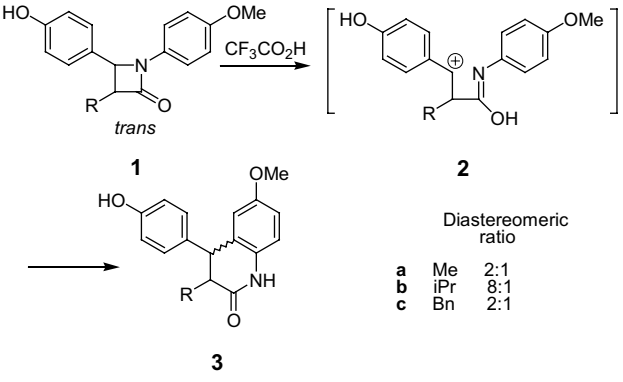
Abstract—Under acidic conditions, the N(1)–C(4) bond of 4-(4′-hydroxyphenyl)-azetidine-2-ones are cleaved with the formation of a stabilized benzylic carbocation intermediates. The intermediates were reduced by silanes or participated in intramolecular or intermolecular Friedel–Crafts reactions to produce tyrosine mimetics.

Due to ring strain, azetidine-2-ones are susceptible to ring cleavage reactions. This property has been exploited by several research groups who have utilized the β-lactam as a synthon for a wide variety of compounds.[1] Ring opening can occur through cleavage of one or more of its bonds. Cleavage of the amide bond by nucleophilic attack at N(1)–C(2) bond is the most common and has been used for the preparation of macrocyclic alkaloids,[2] cyclic polyamines,[3] taxoids,[4] sphingolipids,[5] and β-amino acids.[6] C(2)–C(3)[6a,7] and C(3)–C(4)[8] cleavage reactions have been applied in ring expansion of β-lactams to other heterocycles such as *N*-carboxyanhydrides, pyrazines and oxazines. The C(4)–N(1) bond of 4-aryl-azetidine-2-ones can be cleaved by hydrogenolysis; a reaction that has been applied to synthesize novel amino acids and peptidomimetics.[9] Heteroatom substitution at C(4) renders β-lactams susceptible to 1,4 cleavage under acidic,[10] basic,[11] and neutral[12] conditions, depending on the nature of the functional groups attached at position C(1) and C(3). We recently demonstrated that base-catalyzed ring opening of 4-(4′-hydroxyphenyl)-azetidine-2-ones via bond cleavage at C(4)–N(1) leads to α,β-disubstituted 4-hydroxyhydrocinnamides or tetra-substituted glutarimides, via Michael-type addition to an intermediate quinone methide.[13]

We report here that cleavage of the C(4)–N(1) bond of 4-(4′-hydroxyphenyl)-azetidine-2-ones can also occur under acidic conditions. Treatment of **1a**–**c** with neat trifluoroacetic acid resulted in **3a**–**c** in quantitative yields (Scheme 1). We hypothesize that under acidic conditions the amide bond is protonated and that the C(4)–N(1) bond cleaves with formation of a stabilized benzylic carbocation, **2**. Intramolecular Friedel–Crafts alkylation of the anisidine ring ensues to recyclize the system. Thus, we have provided a novel method for a two-carbon ring expansion of β-lactams.

Starting materials **1a**–**c** were prepared by the Staudinger reaction, that is, the [2+2] cycloaddition of the ketene derived from the corresponding acid chloride and *N*-(4-benzyloxybenzylidene)-*p*-anisidine using Bu_3N in



Scheme 1.

Keywords: β-Lactam; N(1)–C(4) bond; 4-(4′-Hydroxyphenyl)-azetidine-2-one; Trifluoroacetic acid; Peptidomimetic; Friedel–Crafts alkylation.
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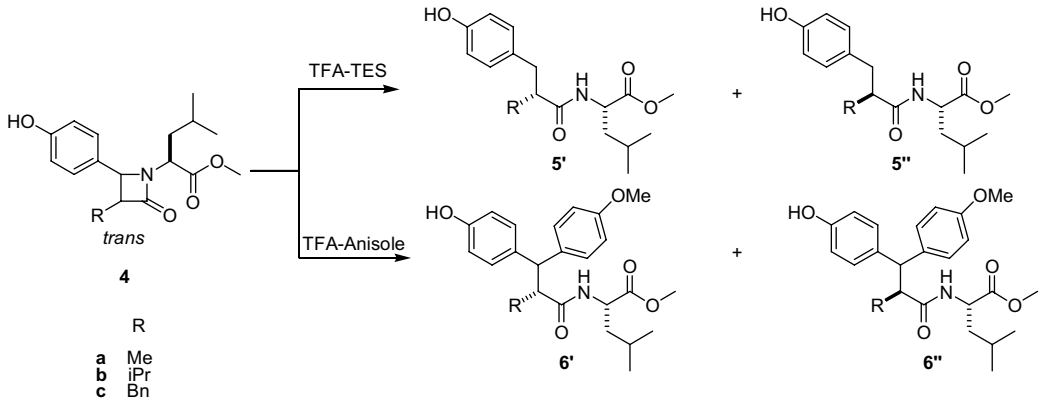

Scheme 2.

refluxing toluene[14] followed by hydrogenolytic removal of the benzyl ether group. This method produces racemic mixtures of *trans* diastereomers[14] ($J_{H3,H4}$ = 2.2 Hz) and **1a–c** were used as such. Formation of **3a–c** was complete within 3 h in quantitative yields as mixtures of two isomers. Both isomers were observed in ^{1}H NMR spectra and resonances could be assigned to each. Diastereomeric ratios, calculated from integrals in the NMR spectra, were dependent on R. The isomers of **3a–c** were difficult to separate by either silica gel chromatography or reverse phase HPLC.[15]

The acid-catalyzed 1,4 cleavage reaction was then used to synthesize 'tyrosyl'-leucine dipeptide mimetics (Scheme 2). Treatment of azetidine-2-ones **4a–c** with trifluoroacetic acid containing either triethylsilane (TES) or anisole gave **5a–c** and **6a–c**, respectively. In the case of compounds **5a–c**, the intermediate carbocation was reduced with TES. In the case of **6a–c**, the carbocation coupled to anisole in an intermolecular Friedel–Crafts alkylation reaction to give the bis-aryl mimetic. Starting compounds **4a–c** were synthesized by the Staudinger reaction as above from *N*-4-benzyloxybenzylidene-L-leucine and the appropriate alkanoyl chloride and were used as equal mixtures of (*S*,*R*,*S*) and (*R*,*S*,*S*) diastereomers (as in **1** the β-lactam was *trans* as $J_{H3,H4}$ was 2.2–2.3 Hz). In each product, two diastereomers were observed in a 1:1 ratio. These mixtures were inseparable by conventional silica gel column chromatography but were separable using C18 reverse phase HPLC.[16,17] In the case of **5a–c**, we do not know the order of elution of the diastereomers, **5′a–c** and **5″a–c**. In the case of **6a–c**, four diastereomers should be formed in theory. The fact that we observe only two is no doubt due to the high degree of similarity of the two aryl rings on C(3) of the propionamide moiety. Again, the order of elution is unknown at this time.

Interestingly, Rosenblum et al. treated a 3-alkyl-4-(4′-hydroxyphenyl)-azetidine-2-one cholesterol absorption inhibitor with 20 mol% of *p*-TsOH·H_2O for 6 h at 60 °C dehydrate, a benzyl alcohol moiety on the C(3) substituent.[18b] No apparent acid decomposition of the ring occurred. McKittrick et al. treated 4-(4′-*tert*-butyldimethylsilyloxyphenyl) β-lactams with 48% aq HF to remove the TBDMS group. The yields of 95% and 97% for the *cis* and *trans* diastereomers, respectively, indicated that no acid catalyzed carbocation formation occurred.[18a] Rosenblum et al. treated 4-(4′-benzyloxyphenyl) β-lactam with the Lewis acid-catalyzed de-benzylation procedure BCl_3·SMe_2. The yield was 68%.[18c] It is unknown whether any Lewis acid-catalyzed carbocation formation occurred. It appears that the acid conditions must be strong enough to protonate the β-lactam amide to allow N(1)–C(4) scission/benzylic carbocation formation to occur.

In summary, we report here a novel reaction for cleavage of the C(4)–N(1) bond of 4-(4′-hydroxyphenyl)-azetidine-2-ones. Because of the presence of the phenolic moiety, this reaction can be used to synthesize compounds to mimic tyrosine in peptide-based drug design research.

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References and notes

1. (a) Alcaide, B.; Miranda, M.; Perez-Castelles, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 297–298; (b) Hess, M. *Ring Enlargement in Organic Chemistry*; VCH verlagsgesellschaft: D-6940 Weinheim (Federal Republic of Germany); (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755–1802; (d) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669–699; (e) Mukherjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547–589; (f) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920; (g) Alcaide, B.; Almendros, B. *Curr. Med. Chem.* **2004**, *11*, 1921–1949.
2. Wassermann, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 462–464.
3. Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, R. *J. Chem. Soc., Chem. Commun.* **1983**, 959–960.