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α-Aminocyclopropanone hydrates: potential transition-state analog inhibitors of serine proteases

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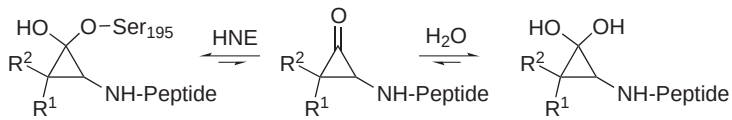
Abstract—The synthesis of two α-aminocyclopropanone hydrates is reported. These synthons could find biological applications by acting as transition-state analog inhibitors of hydrolytic enzymes, such as serine proteases.

Human neutrophil elastase (HNE) is a serine protease involved in the pathogenesis of a wide variety of diseases, such as pulmonary emphysema[1] and inflammatory disorders.[2] Under normal physiological conditions, HNE is regulated by the endogenous macromolecular peptidic structure of α_1-protease inhibitor (α_1-PI). An attractive approach toward prophylactic replacement therapy involves the use of low-molecular-weight synthetic inhibitors.[3] The search for suitable inhibitors of HNE and other serine proteases has been intense during the past ten years and has been reviewed.[4] Up to now, the most efficient designed molecules have made use of an electrophilic carbonyl group. An example of the latter is found in trifluoromethyl ketone,[5–7] which represents an effective transition-state analog of the hydrolytic enzyme. The substrate-based electrophilic carbonyl inhibits the enzyme through the formation of a hemiketal linkage with serine-195. The resulting tetrahedral adduct is presumed to be similar to the tetrahedral intermediate formed during peptide bond hydrolysis.[8]

In this paper, we would like to report the synthesis of two α-aminocyclopropanone hydrates and thereby introduce a new concept in the development of transition-state analog inhibitors of hydrolytic enzymes, such as serine proteases (Scheme 1). Our approach hinges on the facile equilibrium that exists between cyclopropanone hydrates and the parent cyclopropanones.[9] This equilibrium should facilitate the expeditious enzyme-catalyzed nucleophilic addition of serine-195 to the highly reactive three-membered ring ketone, thus leading to the formation of a stable hemiketal adduct.

Our syntheses of the two cyclopropanone hydrates started from the appropriate α-bromo aldehyde that was protected as a 1,2-benzenedimethyloxy acetal. The choice of 1,2-benzenedimethyloxy acetal as hydrate protecting group was governed by its facile removal through catalytic reduction. Bromine β-elimination,[10] followed by catalytic cyclopropanation of the resulting ketene acetal **2a**,**b** with diazoacetonitrile,[11] afforded cyclopropylcarbonitrile **3a**,**b** (**3b** as a 1:1 mixture of diastereomers). The nitrile group was hydrolyzed with KOH in *t*-BuOH[12] and the resulting amide **4a**,**b** was converted to the corresponding methyl *N*-cyclopropylcarbamate **5a**,**b**[13] through DIB-mediated Hofmann



Scheme 1.

Keywords: cyclopropanones; cyclopropanation; enzyme inhibitors.

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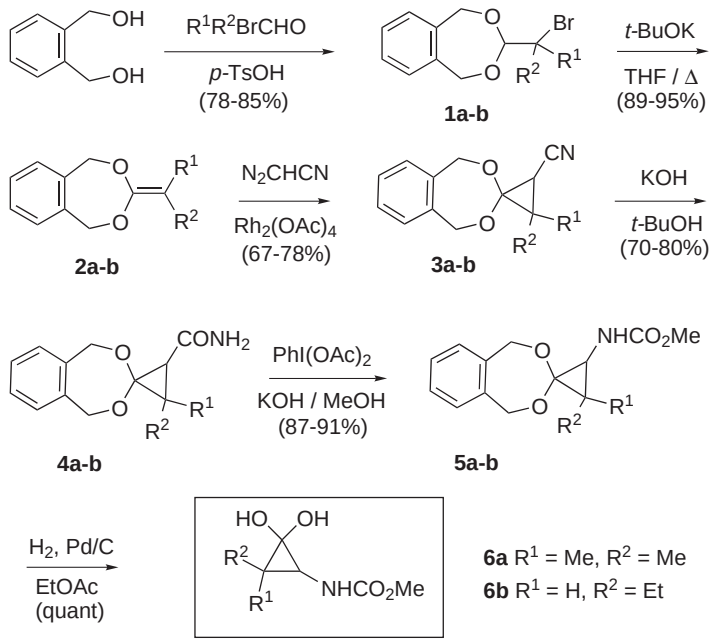

Scheme 2.

rearrangement.[14] It should be noted that the center adjacent to the nitrile moiety in **3b** epimerized during the basic hydration step, leading exclusively to *trans*-cyclopropane **4b**. Finally, catalytic hydrogenolysis over Pd/C in EtOAc afforded the desired α-amino cyclopropanone hydrates **6a**,**b**[15] in quantitative yield (Scheme 2).

A stability experiment was conducted on hydrate **6a** showing that, at room temperature, this compound has a half-life of about 25 h in D_2O (monitored by NMR). The choice of alkyl substituents (for example, **6a**: $R^1 = R^2 = Me$ and **6b**: $R^1 = Et$, $R^2 = H$) on the cyclopropane ring was dictated by the fact that HNE S1-binding subsites (nomenclature of Schechter and Berger)[16] prefer short P1 aliphatic side-chains.[17]

In conclusion, this paper describes a simple route to α-aminocyclopropanone hydrates. We are currently exploring the incorporation of **5a**,**b** into small peptides at the site of the scissile amide unit. In the context of peptide aggregates (which will be selected for optimum interaction with S2–S4 subsites), it is conceivable that, after debenzylation, the resulting peptide-linked cyclopropanone hydrates **6a**,**b** could behave as potent enzyme inhibitors of serine proteases and other hydrolytic enzymes in a fashion analogous to the corresponding trifluoromethyl ketones.

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13. Compound **5a** (white powder, 87% yield): ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13 (s, 3H), 1.31 (s, 3H), 2.71 (d, $J = 4.3$ Hz, 1H), 3.69 (s, 3H), 4.84–5.08 (m, 5H), 7.14–

7.24 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 19.7, 27.5, 41.4, 52.2, 70.7, 71.0, 95.5, 127.0, 127.3, 127.5, 138.0, 138.4, 157.6; HMRS calcd for $C_{15}H_{20}NO_4$ $(M+H)^+$ 278.1392, found 278.1389. Compound **5b** (white powder, 91% yield): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (t, $J=7.3$ Hz, 3H), 1.15–1.19 (m, 1H), 1.47–1.64 (m, 2H), 2.70 (brs, 1H), 3.67 (s, 3H), 4.86–5.09 (m, 5H), 7.16–7.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3, 19.5, 34.7, 39.3, 52.0, 70.9, 71.1, 95.4, 127.1, 127.3, 127.4, 138.1, 138.4, 157.3; HMRS calcd for $C_{15}H_{19}NO_4$ $(M)^+$ 277.1314, found 277.1358. For details on the preparation of **5**, see: Felpin, F. X.; Doris, E.; Wagner, A.; Valleix, A.; Rousseau, B.; Mioskowski, C. *J. Org. Chem.* **2001**, *66*, 305–308.

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15. A typical procedure for the catalytic hydrogenolysis is given for the preparation of compound **6a**: To a solution of **5a** (0.03 g, 0.11 mmol, 1 equiv.) in 2 mL of EtOAc was added 10 wt.% palladium on carbon (0.03 g, 25 mol%). The mixture was stirred vigorously at room temperature under 1 bar of hydrogen pressure for 90 min. The catalyst was filtered off and the solvent was removed under a current of nitrogen. Compound **6a** was obtained in quantitative yield as a colorless liquid: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 (s, 3H), 1.17 (s, 3H), 2.36 (d, $J=2.3$ Hz, 1H), 3.66 (s, 3H), 5.06 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 19.6, 26.8, 41.5, 52.6, 84.7, 159.0. Spectral data for **6b** (colorless liquid, quant): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, $J=7.4$ Hz, 3H), 1.08 (m, 1H), 1.30–1.53 (m, 2H), 2.40 (brs, 1H), 3.66 (s, 3H), 5.25 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3, 19.6, 34.5, 39.6, 52.5, 83.9, 158.8.
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