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Solid and Solution Phase Synthesis of α-Keto Amides via Azetidinone Ring-Opening: Application to the Synthesis of Poststatin

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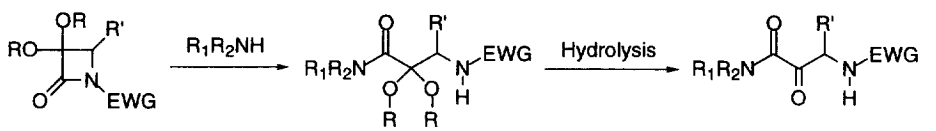
Abstract: 3,3-Diethoxy-N-sulfonyl and carbamoyl azetidin-2-ones undergo efficient ring-opening reaction with various amine nucleophiles. Subsequent acid hydrolysis of the ketal moiety generated α-keto amides in excellent overall yields. The naturally occurring serine protease inhibitor poststatin was synthesized using this ring-opening reaction as the key step.

Keywords: Azetidinone; Cleavage reactions; Keto acids and derivatives; Solid-phase synthesis

α-Keto amides[1] are among the most frequently encountered electrophilic ketone pharmacophores found in protease inhibitors. Even naturally occurring serine protease inhibitors, such as poststatin[2] and cyclotheonamide A[3] have this moiety as a key structural element. Among several methodologies for α-keto amide syntheses reported, notable methods are (1) the oxidation of α-hydroxy amides, and (2) the amidation of α-keto esters with amine nucleophiles.[4] We envisioned that the sequential ring-opening reaction of 3,3-dialkoxy-azetidin-2-ones **I** and hydrolysis of the resulting ketal intermediates **II** could be an efficient and useful means for the preparation of α-keto amides **III** (Scheme 1). Ojima[5] and Palomo[6] have independently demonstrated that 3,4-disubstituted-*N*-(*tert*-butyloxycarbonyl)-azetidinones undergo facile ring-opening reaction with both amine and alcohol nucleophiles. Herein, we wish to report our initial investigations in this area and demonstrate the utility of this methodology in the synthesis of the naturally occuring protease inhibitor poststatin.

Scheme 1



I II III

The racemic 3,3-diethoxy-4-substituted azetidin-2-ones **3** - **7** used in our studies were obtained by the silyl imine-enolate condensation protocol (Scheme 2).[7] Silyl imines (generated from propionaldehyde or benzaldehyde with lithium bis(trimethylsilyl)amide, LiHMDS) were treated with 2 equiv of lithium enolate (generated from ethyl diethoxyacetate with lithium diisopropylamide, LDA) in THF at -78 °C to provide *N*-deprotected azetidinones in good yields (74% for **1**, 68% for **2**). *N*-Protection of azetidinones **1** and **2** with electron-withdrawing groups such as *p*-toluenesulfonyl (*p*-Ts), *p*-nitrobenzenesulfonyl (*p*-NBS), and allyloxycarbonyl (Alloc) groups was carried out using known procedures (Scheme 2).[8,9,10]

With azetidinones **3**, **4**, **5**, and **6** in hand, we next examined their ring-opening reactions with various amine nucleophiles. The results are summarized in Table 1. In a typical experimental procedure for the ring-opening reaction, a mixture of azetidinone (1 equiv) and amine nucleophile (1.1 equiv) in THF was stirred at

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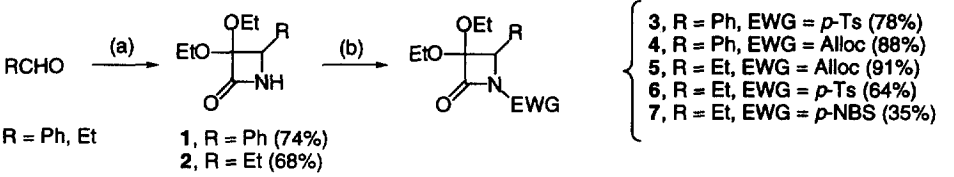
room temperature until the azetidinone was completely consumed (TLC). The crude mixture was then concentrated and directly purified by column chromatography to give the ketal **8** in high yields.

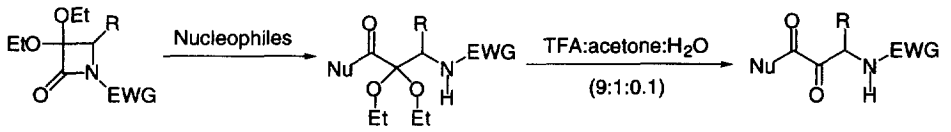
Scheme 2



(a) i. LiHMDS, THF, -30 °C, 1 h, ii. inverse addition to an enolate solution prepared from ethyl diethoxyacetate and LDA, THF, -78 °C, iii. aq. HCl soultion.
(b) NaHMDS, *p*-TsCl or *p*-NBSCl, THF, -78 °C or $ClCO_2CH_2CH{=}CH_2$, DMAP, DBU, DCM.

Both primary and secondary amines (entries a, b, c, d and f) efficiently underwent ring-opening reaction with azetidinones **3**, **4**, **5**, and **6** to yield α-ketal amides **8** (**a-d**, **f**) in excellent yields (87-95%) regardless of the substituents on the nitrigen of the azetidinone. In general, the reactions were complete within 10 h. Ring-opening of azetidinone **5** with an α-branched amino alcohol, L-phenylalaninol was sluggish under these conditions (ca. 20% conversion, entry g). Neither high reaction temperature (in refluxing THF) nor base (Et_3N and DMAP) helped to bring the reaction to a completion. However, this reaction was complete within 4 h under using cyanide catalysis (KCN in DMF or DMA at rt).[6,11,12]

Table 1. Preparation of α-Keto Amides.



3 - 6 **8a - 8j** **9a - 9j**

Entry	Azetidinone	Nucleophile	Conditions	**8** Yield (%)[a]	Product	Yield (%)[a]
a	**3**	*p*-MBA[b]	THF, rt	95	**9a**	87
b	**4**	*p*-MBA	THF, rt	92	**9b**	85
c	**4**	Furfurylamine	THF, rt	87	**9c**	79[g]
d	**4**	Morpholine	THF, rt	95	**9d**	82
e	**4**	L-Val-OMe[c]	KCN, DMF, 70 °C	68	**9e**	71
f	**5**	p-MBA	THF, rt	89	**9f**	84
g	**5**	L-Phenylalaninol	KCN, DMA[e], rt	87	**9g**	74
h	**6**	**10**[d]	THF, 60 °C	-	**9h**	72 (84)
i	**4**	**10**	KCN, NMP[f], 90 °C	-	**9i**	67 (72)
j	**5**	**10**	KCN, NMP, 90 °C	-	**9j**	61 (76)

(a) Isolated yield. The values in parentheses are purity based on the HPLC analysis (C18 column, gradient elution with 0-100% acetonitrile and 0.1% TFA in water, UV detection at 214 nm). (b) *p*-MBA (*p*-methoxybenzylamine). (c) *N*-Methylmorpholine was used to neutralize the amine salt. (d) **10** is Wang resin-bound phenylalanine. (e) DMA (dimethylacetamide). (f) NMP (*N*-methylpyrrolidine). (g) A mixture of **9c** and furan hydrolyzed product was obtained.

Similarly, the sterically hindered amine nucleophile L-valine methyl ester (L-Val-OMe) afforded the ring-open product ketal **8e**, albeit at higher reaction temperature and longer reaction time (KCN in DMF at 60 °C for 2 days, entry e). It is worth mentioning that ring-opening reactions of azetidinones **4** and **5** with bulky nucleophiles appear to be much slower than analogous reactions reported by Ojima[5] and Palomo[6]. We believe that the steric hindrance resulting from disubstitution at C-3 of the azetidinone might be responsible for the relatively slow reaction rate.

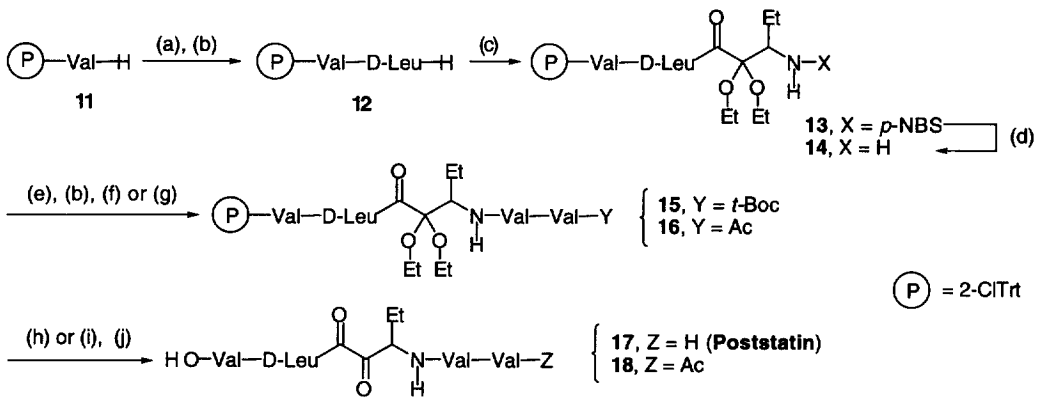
The hydrolysis of ketal intermediate **8** to the final product, α-keto amide **9** initially appeared to be problematic. Several known acid-promoted cleavage conditions[13] employed gave either no product or moderate

conversion (ca. 56% conversion with TFA:H_2O (9:1), at rt for 1 day). Eventually, we found that the addition of acetone is critical.[14] Thus, in a solution of TFA:acetone:H_2O (9:1:0.1), ketals **8** hydrolyze cleanly to provide α-keto amides **9** in good yields. In general, hydrolysis reactions were complete within 12 h at room temperature under these conditions in good yields (71-87%).

Next, the ring-opening reaction of azetidinones was conducted on solid support in order to investigate the feasibility of this methodology for combinatorial library synthesis. First, Wang resin-bound amine **10** (1 equiv) underwent ring-opening reaction with azetidinone **6** (2 equiv) smoothly (THF, 60 °C) to provide the product **8h** (entry h). Sequential resin cleavage (5% TFA in DCM) and hydrolysis (TFA:acetone:H_2O, 9:1:0.1) gave α-keto amide **9h** in 72% isolated yield (based on the initial loading of resin, 84% pure) for three steps. *N*-Alloc-azetidinones, **4** and **5** did not undergo ring-opening reactions under these conditions with **10** (entry i and j). In this case, the *N*-carbamoyl group confers less reactivity on the C=O than the sulfonamide group. Once again, in the presence of ring-opening promoter (1 equiv of resin-bound amine, 3 equiv of azetidinone, and 3 equiv of KCN in NMP (0.1 M) at 90 °C), the reaction provided the desired products **8i** and **8j**. Direct treatment of ketals **8i** and **8j** with a solution of TFA:acetone:H_2O (9:1:0.1) afforded α-keto amides **9i** (67% yield, 72% pure) and **9j** (61% yield, 76% pure), respectively.

In order to demonstrate the utility of the chemistry presented above, we decided to pursue the synthesis of the naturally occuring serine protease inhibitor, poststatin **17** (Scheme 3). The synthesis began with L-Val on 2-ClTrt resin **11**.[15] Amidation of **11** with N-Fmoc-D-Leu-OH by standard protocol (HBTU, HOBt, DIEA, NMP) and deprotection of N-Fmoc group with 20% piperidine in NMP provided the free amine **12**. The key step, azetidinone ring-opening reaction of **12** with 2 equiv of (±)-azetidinone **7** went smoothly (THF, 60 °C, 0.1 M) to give the desire product **13**. HPLC analysis of resin-cleaved crude product **13** (0.5% TFA in DCM, RT, 0.5 h) showed 95% purity (45% isolated yield based on the initial loading of resin **11**).

Scheme 3



(a) Fmoc-D-Leu-OH, HBTU, HOBt, DIEA, NMP. (b) 20% Piperidine, NMP. (c) **7**, THF, 60 °C. (d) PhSH, K_2CO_3, DMF. (e) Fmoc-L-Val-OH, HBTU, HOBt, DIEA, NMP. (f) *t*-Boc-L-Val-OH, HBTU, HOBt, DIEA, NMP . (g) Ac-L-Val-OH, HBTU, HOBt, DIEA, NMP. (h) 20% TFA, DCM. (i) 5% TFA, DCM. (j) TFA:acetone:H_2O (9:1:0.1), rt.

Deprotection of *p*-NBS group of **13** underwent efficiently under the standard Fukuyama protocol[16] (PhSH, K_2CO_3, DMF, rt) to give the free amine **14**. Sequential amidation of **14** with *N*-Fmoc-L-Val-OH, deprotection with 20% piperidine, amidation with *N*-*t*-Boc-L-Val-OH gave the product **15**. Treatment of the resin **15** with 20% TFA in DCM provided both resin-cleaved and t-Boc deprotected product in ca. 14% overall yield. Hydrolysis of the resulting ketal compound turned out to be extremely sluggish.[17] Excess amount of a solution of TFA:acetone:H_2O and longer reaction time (ca. 7 days) allowed ca. 80% conversion of the starting material. Nonetheless the crude product was purified by preparative HPLC to give the desired product, poststatin **17** (30% isolated yield) as a mixture of epimers at the postine[18] residue.

In a similar maner, Ac-capped poststatin **18** was prepared. *N*-Ac-L-Val-OH was used at the final amidation step to serve this purpose. After the amidation (steps e, f, and g in Scheme 3), the resin **16** was cleaved by 5% TFA in DCM (ca. 27% overall yield) and hydrolyzed in a solution of TFA:acetone:H_2O (5 days, 100% conversion) to give the Ac-capped poststatin **18** (46% isolated yield by preparative HPLC) as a mixture of epimers at the postine[18] residue.

In summary, we have developed an expedient method for the preparation of α-keto amides by an azetidinone ring-opening/hydrolysis sequence. This strategy was successfully applied to the synthesis of the

natural product, poststatin and its acylated analogue. Completion of this synthesis on solid support strongly suggests that application of this methodology to the combinatorial synthesis of α-keto amides is feasible.

References and Notes

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    (b) Organic solvent-soluble Et_4NCN could be used instead of KCN. See, Rzasa, R.M.; Shea, H.A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591-592.
12. Additional five α-branched aminoalcohols derived from natural α-amino acids were examined for ring-opening reaction with azetidinone **5**. Under the identical reaction conditions (KCN, DMA, rt), these nucleophiles provided α-diethoxy amides **7** in 91 - 100% crude yield and 53 - 90% purity based on HPLC and LC/MS analyses.
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14. We would like to thank Dr. Matthew Burger, Chiron for his contributions in this area.
15. 2-ClTrt resin was chosen to inhibit the side reaction which generates diketopiperazine.
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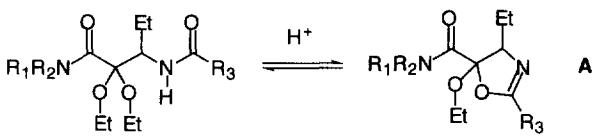
17. Relative to carbamate and sulfonamide ketals, the hydrolysis of amido ketals is found to be much slower. This might be due to the formation of oxazoline intermediate **A**.



18. (S)-3-Amino-2-oxopentanoic acid.
19. **9b**: ^1H NMR (300 MHz, $CDCl_3$) 3.88(s, 3H), 4.36(AB q, J = 14.8, 6.0Hz, 1H), 4.46(AB q, J = 14.8, 6.0Hz, 1H), 4.63-4.65(m, 2H), 5.30(br d, J = 10.6Hz, 1H), 5.39(br d, J = 17.1Hz, 1H), 5.93-6.12(m, 2H), 6.44(br d, J = 7.5Hz, 1H), 6.92(d, J = 8.8Hz, 2H), 7.18(br d, J = 8.3Hz, 3H), 7.43-7.52(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 42.9, 55.3, 59.5, 65.9, 114.1, 117.8, 128.2, 128.4, 128.7, 129.0, 129.1, 132.3, 134.1,154.9, 158.2, 159.1, 192.7; ESMS 383($M+H^+$).