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AN ALTERNATIVE SYNTHESIS OF PEPTIDYL α-KETO-2-OXAZOLINES

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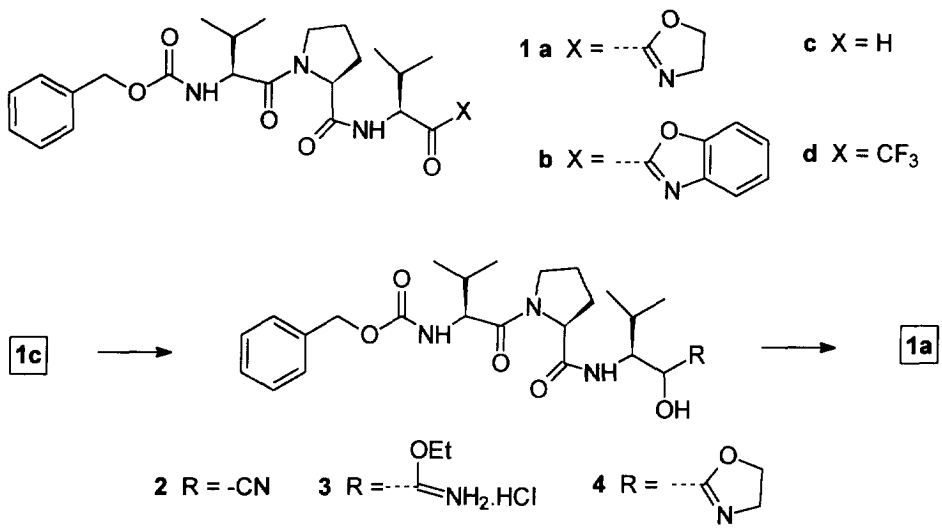
Abstract: Application of Wipf's protocol to generate α-keto-2-oxazolines is described.

Recently, Edwards et al. reported a series of peptidyl α-ketoheterocycles as potent inhibitors of human neutrophil elastase (HNE), a serine protease, believed to be involved in either initiating or contributing to the pathological effects in pulmonary emphysema, rheumatoid arthritis, atheroschlerosis, cystic fibrosis, and other inflammatory disorders.[1] Peptidyl α-ketoheterocycles have also been reported as potent inhibitors against prolyl endopeptidase[2a,b] and thrombin[2c,d,e]. In the HNE enzyme assay, the α-keto-2-oxazoline, **1a** (Scheme 1) was ca. five times more potent than the α-ketobenzoxazole, **1b**. In comparison with other tripeptidyl electrophilic ketone inhibitors of HNE, **1a** was also more potent than corresponding peptidyl aldehyde (**1c**) and trifluoromethyl ketone (**1d**).

Scheme 1 (Edwards et al.[1c])



Synthesis of compound **1a** was initiated from **1c**. Cyanohydrin formation of **1c** generated **2** that was converted to α-hydroxyimidate **3**. Treatment of **3** with 2-aminoethanol generated the α-hydroxy-2-oxazoline **4**. Swern oxidation of **4** generated **1a** (3.08% isolated yield over last two steps[1c]). Our interest in this class of enzyme-reactive group motivated us to seek an alternate synthetic procedure. Several years ago, Wipf et al. reported that treatment of dipeptides (**5–6**) derived from serine or threonine, with Burgess reagent

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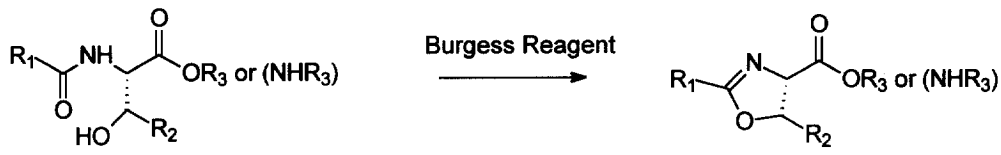
{(methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt} generates the corresponding oxazolines (**7–8**, Scheme **2**).[3]

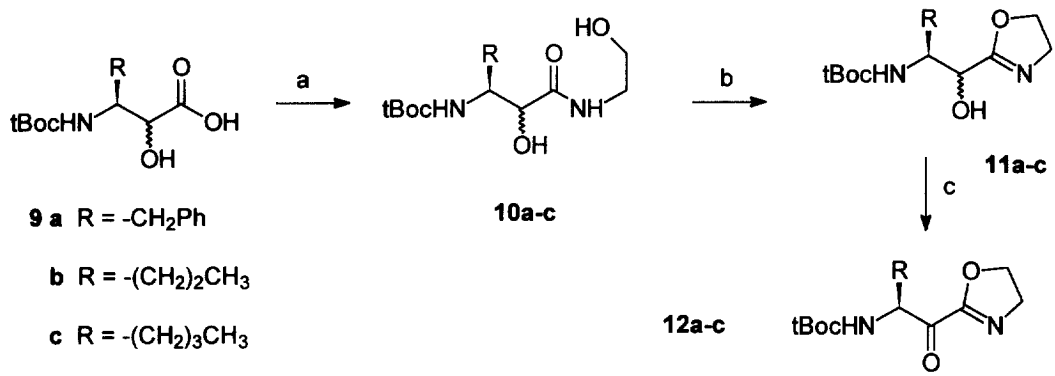
Scheme 2 (Wipf et al.[3])



5 $R_2 = H$; **6** $R_2 = CH_3$ **7** $R_2 = H$; **8** $R_2 = CH_3$

We envisioned applying Wipf's protocol to generate peptidyl α-keto-2-oxazolines. Thus we coupled the α-hydroxyaminoacids[4] (**9a–c**, Scheme **3**) with 2-aminoethanol to produce the corresponding α-hydroxyamides (**10a–c**). Cyclodehydration of **10a–c**, in presence of Burgess reagent, generated α-hydroxy-2-oxazolines **11a–c** (40–43%). Note that the cyclodehydration step involves participation of a primary hydroxyl group in presence of a secondary hydroxyl group. Dess–Martin oxidation[5,6] of **11a–c** gave the desired α-keto-2-oxazolines **12a–c** (55–65%).

Scheme 3



9 a $R = -CH_2Ph$

b $R = -(CH_2)_2CH_3$

c $R = -(CH_2)_3CH_3$

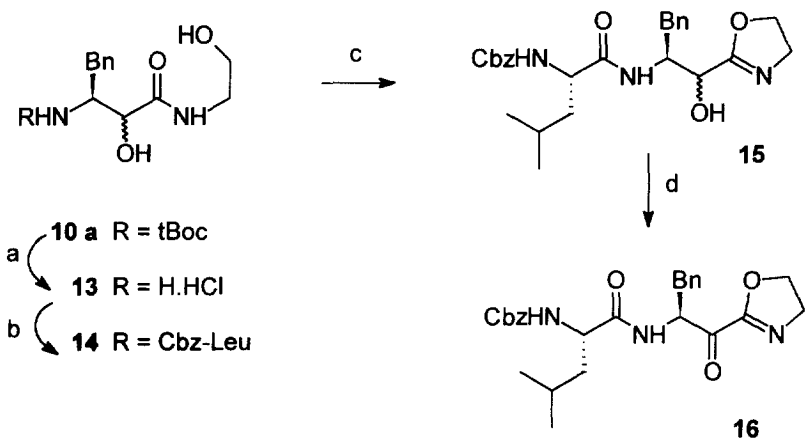
10a-c

12a-c

Reagents: (a) 2-aminoethanol/HOBt/BOP/NMM/DMF, 0 °C to rt, 2 h, 50–75%; (b) Burgess reagent/THF/heat, 1.5 h, 40–43%; (c) Dess–Martin periodinane/methylene chloride, 0 °C to rt, 1 h, 55–65%.

This methodology can also be applied to generate dipeptide α-keto-2-oxazolines; an illustrative example is shown below (Scheme **4**). Thus, compound **10a** was deprotected to generate the amine **13** (as HCl salt) that was subsequently coupled with Cbz-Leu-OH to produce **14**. Cyclodehydration of **14**, in presence of Burgess reagent, yielded **15** that was oxidized to generate the dipeptide α-keto-2-oxazoline **16**. In a similar fashion, utilizing a dipeptide motif, eg. Cbz-Leu-Leu-OH in place of Cbz-Leu-OH, corresponding tripeptide α-keto-2-oxazoline was generated (not shown).

Scheme 4



Reagents: (a) 4 N HCl in dioxane, rt, 1 h, 80%; (b) Cbz-Leu-OH/HOBt/BOP/NMM/DMF, 0 °C to rt, 1 h, 88%; (c) Burgess reagent/THF/heat, 1.5 h, 32%; (d) Dess–Martin periodinane/methylene chloride, 0 °C to rt, 1 h, 68%.

In conclusion, we have described in this *Letter* an alternate synthesis of peptidyl α-keto-2-oxazolines.[7] This method utilizies a cyclodehydration step involving participation of a primary hydroxyl group in presence of a secondary hydroxyl group. Application of this methodology to develop protease inhibitors will be the subject of future reports from our laboratories.

Typical experimental procedures. (a) Synthesis of **10c**: To a cooled (0 °C) solution of **9c** (1.0 g, 3.85 mmol) in anhydrous DMF (10 mL) was added HOBt (0.57 g, 4.22 mmol) and BOP (1.90 g, 4.22 mmol). The mixture was stirred for 10 min and to it added NMM (1.3 mL, 11.6 mmol) followed by 2-aminoethanol (0.30 mL, 4.96 mmol). The cooling bath was removed and the mixture was stirred for 2 h. It was then diluted with ethyl acetate (150 mL) and washed successively with water, 2% citric acid solution, 2% $NaHCO_3$ solution, water and brine. Solvent evaporation gave a crude material which was purified by flash column chromatography (silica gel; eluant: EtOAc) to give 0.88 g (75%) of **10c**, as a mixture of diastereomers (hydroxy bearing carbon center); R_f(EtOAc): 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 and 7.10 (2 sets of broad, 1H); 5.10–3.40 (a series of m, 8H); 3.30 (broad, 1H); 1.80–1.20 (a series of m, 6H); 1.45 and 1.40 (2 singlets, 9H); 0.90 (2 sets of overlapping triplet, 3H); MS (electrospray) *m/e* 305 (M + H), 327 (M + Na).

(b) Synthesis of **11c**: To a solution of **10c** (0.102 g, 0.336 mmol) in THF (3 mL) was slowly added Burgess reagent (0.09 g, 0.367 mmol). The mixture was stirred at room temperature for 10 min and then at 70 °C for 1 h. After cooling, the reaction mixture was poured into a mixture of saturated NH_4Cl (3 mL) and water (3 mL) and extracted into ethyl acetate (2 x 10 mL).[8] The combined organic layer was dried ($MgSO_4$) and concentrated. The crude material was purified by flash column chromatography (silica gel; eluant: 4% MeOH in CH_2Cl_2) to give 0.041 g (43%) of **11c** as a mixture of diastereomers (hydroxy bearing carbon center); R_f(3% MeOH in CH_2Cl_2): 0.21; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 and 4.80 (2 sets of d, 1H); 4.40–4.20 (overlapping m, 3H); 4.00–3.70 (a series of m, 3H); 3.60 (broad, 1H) 1.70–1.20 (a series of m, 6H); 1.45 and 1.40 (2 singlets, 9H); 0.90 (2 sets of overlapping triplet, 3H); MS (electrospray) *m/e* 287 (M + H).

(c) Synthesis of **12c**: To a cooled (0 °C) solution of **11c** (0.12 g, 0.4 mmol) in methylene chloride (5 mL) was slowly added Dess–Martin periodinane reagent (0.34 g, 0.8 mmol). The cooling bath was removed and the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (50 mL) and a 10% $Na_2S_2O_3$ solution (15 mL) was added to the reaction flask and the mixture was stirred vigorously for 15 min. Organic layer was separated and washed successively with 10% $Na_2S_2O_3$ solution (4 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), and brine. Solvent evaporation gave 0.063 g (55%) of **12c**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 and 5.00 (overlapping m, 2H); 4.30 (t, 2H); 4.10 (t, 2H); 1.60–1.20 (a series of m, 6H); 1.40 (s, 9H); 0.90 (t, 3H); MS (electrospray) *m/e* 285 (M + H), 307 (M + Na).

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