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Solid-phase synthesis of peptidyl α-keto heterocycles

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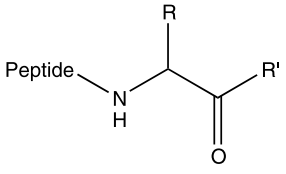
Abstract—The synthesis of structurally diverse peptidyl α-keto heterocycles via a solid-phase methodology is reported.

Cysteine and serine proteases have been implicated in the etiology of various disease states.[1] Identification of selective and reversible inhibitors of such proteases would be of great therapeutic benefit.[2] Over the past decade a number of peptide based inhibitors of serine and cysteine proteases have been taken into clinical development.[3] Notable among these are the peptidyl aldehydes (**1**), α-keto esters (**2**), α-keto amides (**3**) and α-keto heterocycles (**4**).[4,5] Libraries of this class of molecules could be valuable in identifying novel lead structures against new members of the protease class of enzymes. Although there have been a few reports of solid-phase synthesis of peptidyl aldehydes[6] and α-keto amides[7] there has been no reports of solid-phase synthesis of other classes of reversible serine/cysteine protease inhibitors. This is probably due to the lack of suitable linkers that would allow easy C-terminal modification of resin bound amino acids/peptides.



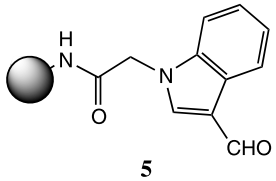
1 R' = H

2 R' = CO_2R

3 R' = C(O)NHR

4 R' = Het

Recently, Estep et al.[8] reported the utility of a novel indole linker **5** in solid-phase synthesis of secondary amides and sulfonamides. We envisioned that this linker could be used for the solid-phase synthesis of a number of peptide based reversible inhibitors of serine and cysteine proteases. Herein we report the first solid-phase approach to peptidyl α-keto heterocycles **4** based on the indole linker. A key aspect of this approach is the ability to modify simultaneously both the C and N terminal of an immobilized aminoacid.



5

The cornerstone of our approach is the resin bound Weinreb amide **8** which was synthesized as shown in Scheme 1.[9,10] Thus reductive amination[11] of aldehyde resin **5** with a number of aminoacid allyl esters provided immobilized secondary amines **6** in excellent yield. Surprisingly, coupling of a second amino acid to **6** proved to be quite difficult. After considerable experimentation, racemization free coupling was achieved using 10–15 equiv. of appropriate *N*-protected amino acid and DIC/HOAt as the coupling agent.[12] Under these conditions near quantitative yield of dipeptide ester **7** was realized. The latter was subjected to Pd(0) catalyzed deallylation[13] and the resulting acid was coupled with *N*,*O*-dimethylhydroxylamine hydrochloride (DCC, DMAP)[14] to provide the requisite Weinreb amide **8**. Treatment of **8** with a large excess (30–40 equiv.) of aryl and heteroaryl lithiums (generated from the corresponding heteroarene using *n*-BuLi) at –78°C to room temperature led to resin bound ketones **9**. Finally cleavage from solid support using 1:1 TFA/DCE provided peptidyl α-keto heterocycles **4**.[15] Unfortunately, the products were found to be extensively racemized (30–40%) at the carbon α to the ketone carbonyl group. All attempts to suppress such racemization (shorter reaction times, less amount of organolithium and lower reaction temperatures) proved futile. The origin of this racemization is unclear. It is conceivable that it occurs during the cleavage of **4** from the solid support and not during the addition of organometallic reagent to **8**.[16]

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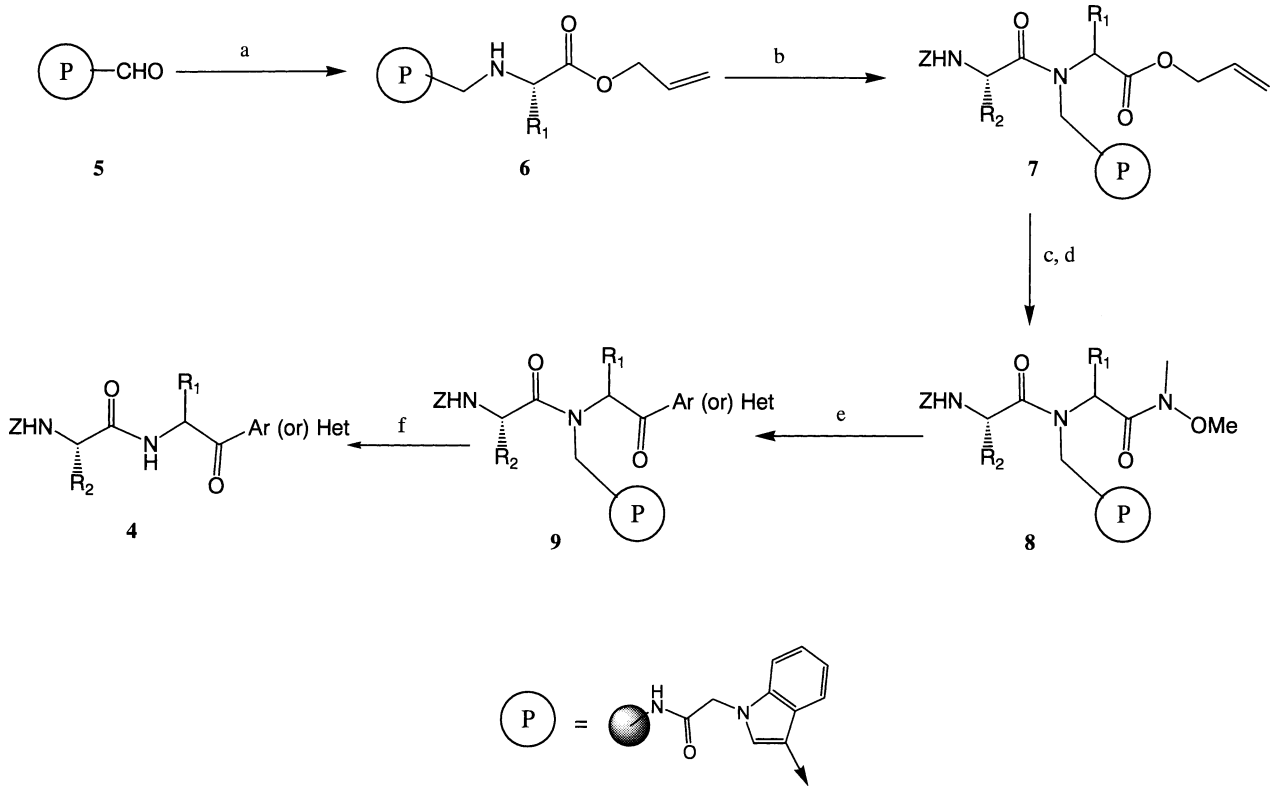
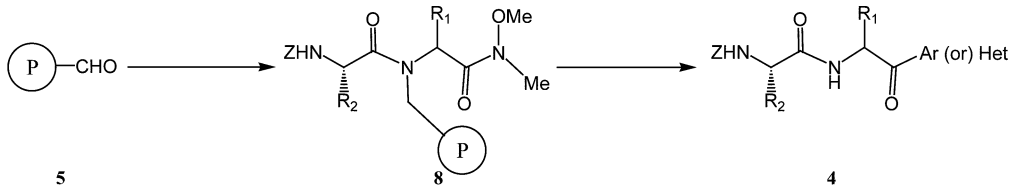
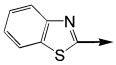
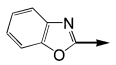
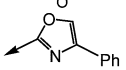
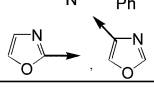


Scheme 1. *Reagents and conditions*: (a) i. H-AA-allylester/TMOF/MeOH, rt, ii. $NaCNBH_3$/MeOH/rt; (b) Z-AA-OH, DIC, HOAt, DMF; (c) THF, CH_3CN, $Pd(PPh_3)_4$, morpholine; (d) DCC, NMe(OMe)·HCl, DMAP; (e) PhLi (or) Het-Li, THF, −78°C to rt; (f) 1:1 TFA/DCE.

Table 1.



Product	R_1	R_2	Ar (or) Het	Purity[a]	Yield(%)[b]
4a	CH_2Ph	CH_2Ph	Ph[c]	95	45
4b	CH_2CH_2Ph	CH_2Ph		75	30
4c	CH_2CH_2Ph	CH_2Ph		85	50
4d	CH_2CH_2Ph	CH_2Ph		90	25
4e	CH_2CH_2Ph	CH_2Ph		75	30
4f	CH_2CH_2Ph	CH_2Ph		60	10
4g	CH_2CH_2Ph	CH_2Ph		75	50
4h	CH_2CH_2Ph	CH_2Ph		75	40[d]

[a]Purity of crude product determined by reverse phase HPLC [b]Isolated by either column or Preparative thin layer chromatography. [c]The reaction was found to proceed better with PhMgCl as the organometallic reagent than with PhLi. [d]Combined yield for 2 and 4 substituted oxazolyl ketone

As seen from Table 1 the synthetic route shown above works well with a variety of heteroaryl lithiums. Noteworthy is oxazolyl lithium which provided an inseparable 1:1 mixture of 2- and 4-substituted oxazole ketones **4h**. This is possibly due to reaction of **8** with both 2-lithiooxazole and the corresponding ring-opened lithium enolate.[17]

In summary, a general procedure for solid-phase synthesis of peptidyl α-keto heterocycles from the corresponding aminoacid allyl esters has been developed. The procedure has the potential to be expanded for the synthesis of other classes of reversible inhibitors of serine and cysteine proteases.

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10. General procedure for the synthesis of ketone **4**: To a suspension of indole resin **5** (5.0 g, 3.6 mmol) in 2:1 trimethylorthoformate (TMOF):MeOH (75 mL) was added aminoacid allyl ester-*p*-toluene sulfonate (18.0 mmol) and the mixture was shaken gently overnight. A solution of $NaCNBH_3$ (75 mmol) in TMOF (75 mL) was added, shaken for 6 h, filtered, washed (1:1 THF/H_2O, DMF, THF and MeOH) and dried to give resin bound amine **6**. An aliquot was acylated (Ac_2O, DIEA, DCM, DMAP) and cleaved to give the corresponding AcNH-AA-O-Allyl. Based on the yield of the latter, the loading was determined to be nearly quantitative with all the amino acids used.
To Z-AA-OH (20.0 mmol) in 4:1 DCE:DMF (50 mL) was added HOAt (20.0 mmol) followed by DIC (20 mmol). After stirring for 20 min, resin **6** (1.6 mmol) was added. The resulting mixture was shaken at rt overnight, filtered, washed and dried to give dipeptide ester **7**. An aliquot was cleaved (1:1 TFA/DCE, 1 h) to determine the loading. In every instance the loading was found to be >95% and the purity >99% (^1H NMR and MS).
To a suspension of **7** (1.0 mmol) in 2:1 THF:CH_3CN (30 mL) was added Pd $(PPh_3)_4$ (0.05 g) and morpholine (4 mL). The resulting mixture was shaken at rt for 12 h, filtered and washed. The resulting resin bound acid was suspended in dichloroethane (60 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (2.7 g, 30 mmol), DCC (5.6 g, 30 mmol) and DMAP (0.25 g, 2 mmol) were added. After shaking at rt overnight, the resin was collected by filtration, washed and dried to give Weinreb amide **8** in near quantitative yield (loading determined by cleaving an aliquot from solid support using 1:1 TFA:DCE).
To a solution of 3.0 mmol of the aryl lithium (generated from the corresponding arenes according to literature procedures) at −78°C was added **8** (0.15 g, 0.07 mmol). After stirring at rt overnight, the resin was collected by filtration, washed and dried to give **9**. To a suspension of **9** in DCE (1 mL) was added TFA (1 mL) and shaken at rt for 1h, filtered and washed with DCE (3×2 mL). The combined filtrates were concentrated in vacuo and the residue was purified by preparative layer chromatography to give **4**.
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15. All compounds were characterized by ^1H NMR and MS.
16. Synthesis of compound **4e** in solution phase by treatment of Z-Phe-HPhe-Weinreb amide with a large excess (15–20 equiv.) of benzthiazolyl lithium showed no racemization, suggesting that the racemization observed in SPS probably occurred during cleavage of the products from solid support. Also, all attempts to prepare benzoxazole **4f** by addition of benzoxazolyl lithium to Z-Phe-HPhe-Weinreb amide gave none of the desired product, thus establishing the power of this solid-phase approach to peptidyl α-keto-heterocycles.
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