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Solid Phase Synthesis of β-Lactams *via* the Staudinger Reaction

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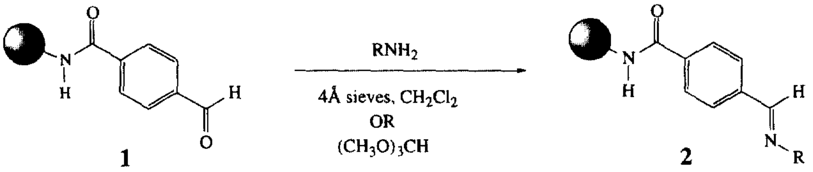
Abstract: The synthesis of *cis*-azetidinones on solid support *via* the Staudinger reaction is described. The final products are obtained in high purity with no purification required.

Solid phase synthesis is increasingly becoming more popular as a standard technique for the generation of individual compounds but also for diverse mixtures of compounds.[2] Screening of individual synthetic molecules combined with natural product collections[3] has long been recognized as an extremely applicable protocol for the discovery of lead structures in drug research. The advent of combinatorial synthesis allows the generation of diverse libraries of compounds. This, in collaboration with high throughput screening has also been identified as a valuable tool by the pharmaceutical industry for the discovery of new leads.[4]

Since the initial discovery of β-lactams and their subsequent importance as antibiotics, numerous publications have appeared pertaining to their synthesis and biological activity.[5] Herein we describe the synthesis of β-lactams *via* [2+2] Staudinger reaction[5] on solid support with the aim of developing methodology for the rapid synthesis of combinatorial libraries. β-Lactams can be formed by the reaction of imines with acid chlorides in the presence of tertiary amine base *via* the generation of ketene intermediates.[5]

The imine component was synthesized by the reaction of various primary amines with resin bound *para*-carboxyaldehyde **1**. Thus, treatment of the aldehyde (resin loading of approximately 0.52mmol/g) with excess amine (typically 10 molar equivalents) in anhydrous dichloromethane in the presence of molecular sieves or trimethylorthoformate[6] afforded a variety of imines **2**, **Scheme 1**. The resin bound imines were isolated by filtration, excess amine was simply removed by washing with dichloromethane and after drying the resin was used for subsequent lactam formation. The Staudinger reaction[7], for the formation of the desired azetidinone **3**[9], was accomplished by the treatment of the imine in dichloromethane with acetoxyacetyl chloride in the presence of triethylamine at room temperature or 0°C, **Scheme 2**. Typically in solution phase this cycloaddition



Scheme 1

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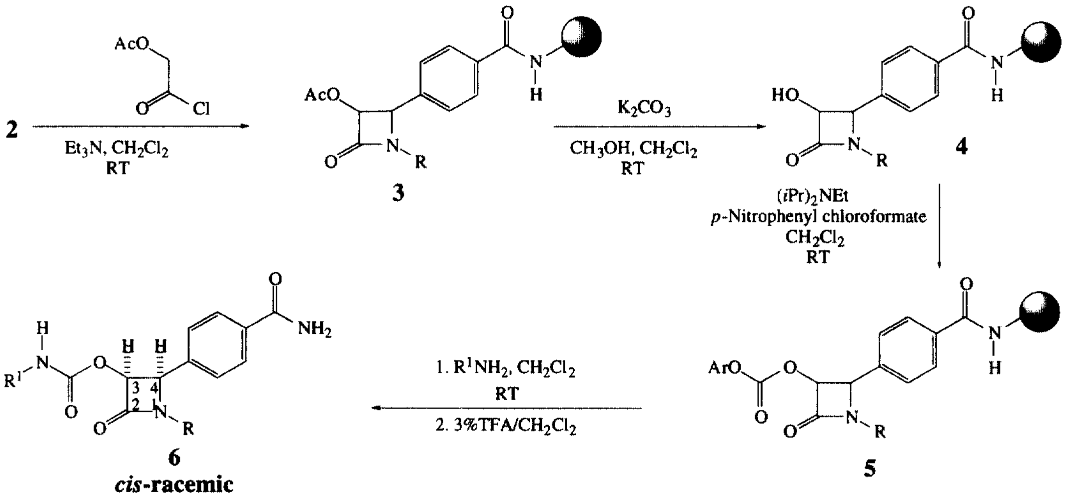
favorably occurs at 0°C and requires chromatographic purification, this problem is eliminated by solid phase synthesis. Initial NMR studies of the products from the Staudinger reaction indicated that only the *cis* azetidinones were produced, the coupling constant between 3H-4H being 5.3Hz. The acetoxy group was removed under mild conditions employing potassium carbonate in methanol and dichloromethane at room temperature overnight.[8] We found that employing more than 1.3 equivalents of potassium carbonate led to the alcoholysis of the azetidinone ring. In addition, the use of sodium methoxide was explored for removal of the acetoxy group however, this proved to be less efficient. The structure of 3-hydroxy azetidinone derivative **4**[9] was confirmed by NMR and mass spectrometry data. Reaction of azetidinone **4** with *p*-nitrophenyl chloroformate in the presence of *N,N*-diisopropylethylamine in dichloromethane afforded the carbonate derivative **5**[8]. The final step, formation of the carbamate **6**,[9] was performed by treatment with primary or secondary amines in dichloromethane, **Scheme 2**. This reaction in general was able to tolerate a large excess of amine with no undesirable cleavage of the azetidinone amide bond being observed.

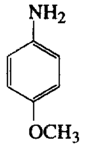
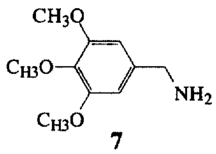
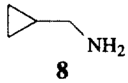
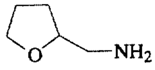
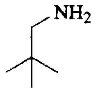
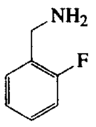
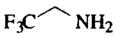
In each step of the synthesis, an aliquot of the desired product was cleaved from the resin upon treatment with 3% TFA in dichloromethane for 15 min, and the isolated products were analyzed by HPLC, NMR and mass spectrometry.



Scheme 2

Table 1 summarizes some of the initial results we have obtained by application of the above methodology. As can be observed the yields indicate that the solid phase synthesis of the azetidinone occurs efficiently. Imines were generated from a range of amines such as alkyl, aryl and anilines. Only electron deficient heterocyclic amines proved to be problematic. In the context of this paper 4 amines are exemplified for imine formation. The carbamate formation step is equally consistent with the use of either primary or secondary amines; again only data for 3 amines is illustrated in this communication. Thus 3,4,5-trimethoxybenzylamine **7**, aminomethylcyclopropane **8** and tetrahydrofurfurylamine **9** were observed to react under identical conditions.

Table 1. Yields and purity from the Staudinger reaction and subsequent steps.

RNH_2	Yield^a% **3** HPLC^b	Yield^a% **4** HPLC^b	Yield^a% **5** HPLC^b	R^1NH_2	Yield^a% **6** HPLC^b
	96 100	92 100	93 100	 **7**	88 100
				 **8**	85 92
				 **9**	89 100
	94 100	90 100	90 92	**7**	80 90
				8	86 95
				9	79 93
	90 100	92 90	87 96	**7**	84 100
				8	84 93
				9	78 100
	89 98	85 99	80 95	**7**	79 92
				8	83 94
				9	80 96

^{a}Yield of isolated product. ^{b}HPLC purity.

Thus, we have demonstrated the successful application of the Staudinger cycloaddition on solid support. As compared to the homogeneous counterpart, undesirable product formation can be avoided and side products resulting from the reaction solution can be washed away from the solid support.

We are currently investigating the application of this methodology towards the generation of diverse combinatorial libraries.

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9. Selected experimental procedures for 2-oxoazetidine-1-(*p*-methoxyphenyl) (RNH$_2$, 4-methoxyaniline) derivative. **Preparation of 3**. To a suspension of the imine **2** (1.0 equiv. 500mg, 0.52mmol/g), triethylamine (3.0 equiv. 110μL) in dichloromethane (6mL) was added acetoxyacetyl chloride (3.0 equiv. 84μL). The resultant mixture was shaken overnight, filtered, washed with dichloromethane and vacuum dried. The resin (60mg) was treated with a 3% solution of TFA in dichloromethane (2mL) and the suspension shaken for 15min. Filtration and concentration *in vacuo* produced a white solid, this was identified as the desired azetidinone **3** (10.6mg, 96%) by analysis of NMR and mass spectrometry data. ^{1}H NMR (Acetone-d$_6$) 1.65 (3H, s), 3.72 (3H, s), 5.61 (1H, d, J=5.3Hz), 6.03 (1H, d, J=5.3Hz), 6.90 (2H, d, J=9.2Hz), 7.30 (2H, d, J=9.2Hz), 7.40 (2H, d, J=9.2Hz), 7.95 (2H, d, J=9.2Hz); *m/z* (Ion spray) 355 (MH$^+$, 100%). **Preparation of 4**. A mixture of azetidinone **3** (1.0 equiv. 420mg), potassium carbonate (1.3 equiv. 39mg), methanol (1.8mL) and dichloromethane (6mL) was shaken overnight. The reaction mixture was decanted carefully so that the excess potassium carbonate remained in the reaction vial and after washing with dichloromethane the resin was dried under vacuum. A small quantity of the resin (60mg) was cleaved as described above to afford derivative **4** (8.9mg, 92%). ^{1}H NMR (Acetone-d$_6$) 3.73 (3H, s), 5.30 (1H, d, J=5.2Hz), 5.40 (1H, d, J=5.2Hz), 6.85 (2H, d, J=9.2Hz), 7.30 (2H, d, J=9.2Hz), 7.44 (2H, d, J=9.2Hz), 7.90 (2H, d, J=9.2Hz); *m/z* (Ion spray) 313 (MH$^+$, 100%). **Preparation of 5**. To a suspension of the 3-hydroxy lactam **4** (350mg) in dichloromethane (5mL) was added *p*-nitrophenyl chloroformate (5.0 equiv. 183mg) and *N,N*-diisopropylethylamine (5.0 equiv. 160μL). The mixture was shaken overnight, filtered, washed with dichloromethane and the isolated resin dried. A sample of resin (60mg) was cleaved with 3% TFA to give resin-free azetidinone **5** (13.9mg, 93%). ^{1}H NMR (Acetone-d$_6$) 3.70 (3H, s), 5.79 (1H, d, J=5.2Hz), 6.10 (1H, d, J=5.2Hz), 6.90 (2H, d, J=9.2Hz), 7.15 (2H, d, J=9.2Hz), 7.31 (2H, d, J=9.2Hz), 7.52 (2H, d, J=9.2Hz), 8.0 (2H, d, J=9.1Hz), 8.25 (2H, d, J=9.1Hz); *m/z* (Ion spray) 477 (MH$^+$, 100%). **Preparation of 6**. A mixture of azetidinone **5** (1.0 equiv. 100mg), 3,4,5-trimethoxybenzylamine (10.0 equiv. 103μL) and dichloromethane (3mL) was shaken at room temperature overnight. The suspension was filtered, washed with dichloromethane and dried under vacuum. The product **6** (14.6mg, 88%) was obtained by cleaving from the resin (60mg) with a 3% TFA solution in dichloromethane. ^{1}H NMR (Acetone-d$_6$) 3.70 (3H, s), 3.78 (9H, s), 4.05 (2H, br t), 5.61 (1H, d, J=5.6Hz), 6.10 (1H, d, J=5.6Hz), 6.46 (2H, s), 6.89 (2H, d, J=9.4Hz), 7.28 (2H, d, J=9.4Hz), 7.41 (2H, d, J=9.4Hz), 7.90 (2H, d, J=9.4Hz); *m/z* (Ion spray) 535 (MH$^+$, 100%).