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Reports

Versatile and Efficient Solid-Supported Synthesis of C3-Anchored Monocyclic β-Lactam Derivatives

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The effectiveness of β-lactam compounds in a large number of clinically important therapeutic areas has been clearly demonstrated. Because of their high efficacy and extremely safe toxicological profile, the β-lactam skeleton (azetidin-2-one) is present in several widely used families of antibiotics, such as penicillins, cephalosporins, carbapenems, carbacephems, and monobactams.[1] Moreover, β-lactam compounds have been shown to possess biological activities as inhibitors of prostate specific antigen,[2] thrombin,[3] human cytomegalovirus protein,[4] human leukocyte elastase,[5] cysteine protease,[6] and cholesterol absorption.[7] The therapeutic importance of this structure is also clear from recent reports about β-lactams related to the treatment of cancer[8] and neurological diseases.[9] As a result, the search for new β-lactam compounds with potential clinical usefulness will continue in future years.

The applicability of combinatorial chemistry and related methodologies to the chemistry of the β-lactams has been demonstrated by research groups around the world.[10] The Staudinger reaction[11] is the most frequently used strategy for the construction of the β-lactam ring not only in solution but also in solid-phase chemistry. The most widely accepted mechanism for the Staudinger reaction[12] involves the 2 + 2 cyclization reaction between an in situ-generated ketene (**II**) and an imine (**III**) to give rise to a zwitterionic intermediate (**IV**). A conrotatory electrocyclic ring closure of **IV** leads to the final β-lactam products that can be cis (**V**), trans (**VI**), or a mixture of both (Scheme 1).

Ketenes are usually generated by elimination of an activated carboxylic acid (**I**) in the presence of a base.[13] Despite some success in the development of the solid-phase version of the Staudinger reaction, all the approaches described so far are based on polymer-bound imines.

As part of our interest in the application of solid-phase chemistry to azetidin-2-one and related compounds,[14] we describe herein the first solid-phase Staudinger reaction based on immobilization of the activated carboxylic acid. This approach led to the development of a strategy for the preparation of C3-anchored β-lactam derivatives that offers new alternatives of functionalization at N1 and C4 of the ring.

We began our studies by evaluating the most suitable linker for the solid-supported strategy. First, we considered the use of a diethylsilyloxy linker (PS-DES resin). Thus, (4-diethylsilylbutyl)polystyrene resin (**1**) was activated by chlorination with *N*-chlorosuccinimide (Scheme 2).[15]

Formation of chloride **2** was evident from the absence of the Si−H stretch (IR 2100 cm^{-1}). Coupling of **2** with methyl 4-hydroxyphenoxyacetate (**3**) was carried out in the presence of imidazole and confirmed by gel-phase ^{13}C NMR of PS-DES resin **4**. The hydrolysis of resin-bound ester was efficiently achieved using trimethyltin hydroxide (TMTOH)[16] to give the corresponding immobilized carboxylic acid **5**.

For the key Staudinger reaction, activation of the carboxylic acid **5** by Mukaiyama's reagent (**6**) was considered.[17] The addition mode was critical to achieve good results. When a suspension of resin **5**, reagent **6**, and triethylamine were refluxed in chloroform for 2 h before the addition of *N*-(4-methoxybenzylidene)-benzylamine **7aa**, the reaction was unsuccessful, even after the mixture was refluxed for another 2 h. The resin-bound β-lactam **8aa** was finally obtained by treatment of **5** with triethylamine (6 equiv), imine **7aa** (5

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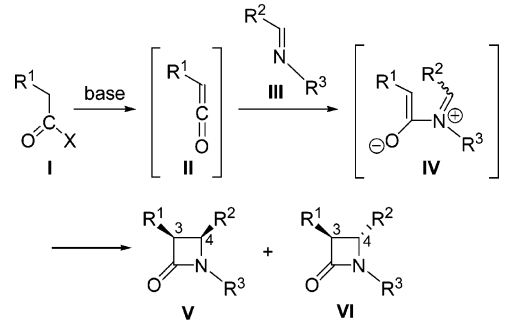
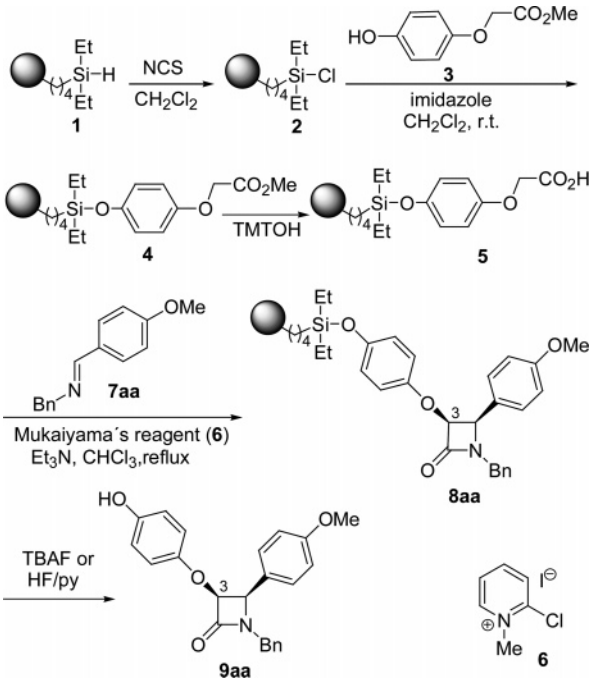
Scheme 1



Scheme 2



equiv), and Mukaiyama's reagent (**6**) (5 equiv), in that order, followed by a reflux in chloroform for 2 h and exposure of the resin to the same cycloaddition conditions to guarantee the β-lactam construction. Cleavage from the resin was accomplished by two different methods: TBAF in THF and HF/pyridine. In both cases, the *cis*-β-lactam **9aa**[18] was obtained in a 12−14% isolated yield for the four reaction steps (based on the manufacturer's loading of the PS-DES resin).

Because of this low yield, we decided to carry out a different anchoring strategy, using Wang resin as support. The methyl 4-hydroxyphenoxyacetate (**3**) was immobilized to Wang resin under modified Mitsunobu conditions (TMAD, Bu_3P)[19] to yield the resin-bound ester **10** (Scheme 3).

The saponification of **10** with potassium trimethylsilanoate gave the corresponding immobilized carboxylic acid **11**[20] which, in turn, was subjected to the solid-phase version of the Staudinger reaction, again using the Mukaiyama's reagent (**6**) as the activating agent. Formation of the β-lactam **12aa** (R_1 = *p*-methoxyphenyl, R_2 = benzyl) was corroborated by FT-IR and gel-phase ^{13}C NMR. Treatment of resin **12aa** with 10% trifluoroacetic acid in CH_2Cl_2 for 1 h at room temperature was found to be a very efficient procedure for the cleavage, affording the trisubstituted *cis*-β-lactam **9aa** in a

Scheme 3

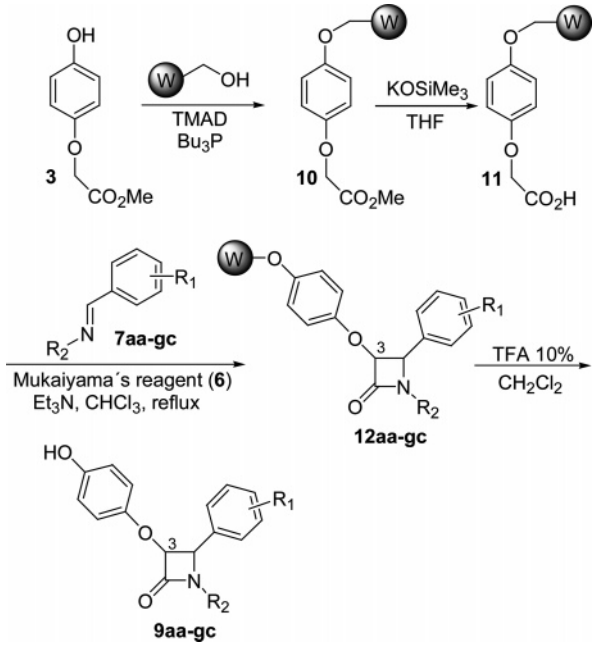


Table 1. Solid-Phase Synthesis of C3-Anchored β-Lactam Compounds

entry	product	R_1	R_2	cis/trans ratio	yield (%)[a]
1	**9aa**	4-MeO	Bn	cis	47
2	**9ba**	4-Br	Bn	cis	53
3	**9ca**	2-Br	Bn	cis	57
4	**9da**	H	Bn	cis	50
5	**9ea**	4-Cl	Bn	cis	37
6	**9fa**	4-Me	Bn	cis	52
7	**9ga**	4-NO_2	Bn	cis	54
8	**9ab**	4-MeO	4-MePh	2:1 cis/trans[b]	27
9	**9bb**	4-Br	4-MePh	3:1 cis/trans[b]	25
10	**9ac**	4-MeO	4-MeOPh	6:1 cis/trans[b]	39
11	**9gc**	4-NO_2	4-MeOPh	7:1 cis/trans[b]	57

[a] Overall isolated yield after flash chromatography (based on the initial loading level of Wang resin). [b]Determined by ^1H NMR of the crude reaction mixtures prior to purification.

47% overall yield after isolation by column chromatography (based on the initial loading level of the Wang resin).

Having optimized the conditions for β-lactam solid-phase synthesis and cleavage, we decided to carry out the synthesis of an array of β-lactams employing imines with diverse stereoelectronic and steric characteristics (Table 1).[21] The expected products were obtained in good overall isolated yields for the five reaction steps on solid phase (25−57%).

According to a recent study on the ketene−imine mechanism,[12a] after the initial attack of the imine nitrogen at the central carbon of the ketene to form the zwiterionic intermediate, a conrotatory ring closure exclusively generates the *cis*-β-lactam, unless an isomerization of the zwiterionic intermediate ocurrs. The competition between both pathways is mainly controlled by the electronic effect of the substituents of ketenes and imines and the steric hindrance of the N-substituent of the imines.

Electron-donating substituents on the ketene and electron-withdrawing substituents on the imine speed up the direct ring closure, while electron-withdrawing ketene substituents and electron-donating imine substituents slow the direct ring

closure, favoring isomerization of the zwiterionic intermediate and increasing the relative amount of the trans isomer. As reported in Table 1, the cis−trans stereoselectivity found in the solid-phase synthesis of C3-anchored β-lactams is in agreement with that expected for the ketene−imine mechanism,[12a] giving support to the formation of the resin-bound ketene intermediate during the Staudinger reaction.[22] The corresponding *cis*-β-lactams were obtained exclusively in most of the cases because of the strong effect of the electron-donating substituent at position 3. However, this effect can be partially reversed by the use of imines derived from electron-donating aromatic amines (entries 8−11). Apart from the expected electronic effects, the relatively bulkier *N*-aryl substituent at the imine could play an important role in the control of the stereochemistry of the β-lactam product.[23]

Interestingly, the use of *o*-bromobenzaldehyde (entry 3) did not seem to affect the reaction yield. It was expected that ring closure of **IV** (Scheme 1) would be more difficult for such a sterically hindered aldehyde.

Additional support for the ketene mechanism can be found in reactions with electronically deficient imines, where it was observed they would hardly react directly with an activated acid.[24] In our hands, both imines with electron-donating or electron-withdrawing groups reacted with similar efficiency (see entries 1 and 7). To our knowledge, there is no literature precedent for the synthesis of β-lactams using an immobilized ketene, and only few reports on the application of polymer-bound ketenes for intermolecular reactions.[25]

In summary, we have described here a new approach for the preparation of biologically promising β-lactam derivatives on a solid support. This methodology is based on the Staudinger reaction between an immobilized ketene and different imines. Of the two linkers tested, the Wang resin proved to offer better results than the diethylsilyloxy linker, allowing an efficient reaction sequence giving good overall isolated yields of the desired β-lactams. The cis−trans stereoselectivity of the products was in agreement with that expected for the ketene−imine mechanism. This approach will facilitate the development of solid-phase libraries of biologically interesting multicyclic β-lactam compounds via the introduction of diversity at N1 and C4 of the β-lactam ring.

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Supporting Information Available. Experimental procedures, spectroscopic data, ^{1}H NMR and ^{13}C NMR spectra of new compounds, and the ^{13}C NMR gel-phase spectra of β-lactam **9da**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Similar results were obtained with TMTOH.

(21) Typical procedure: Wang resin (167 mg, 0.96 mmol/g) was swollen in a 1:1 mixture of THF/CH_2Cl_2 (5 mL) under a nitrogen atmosphere. TMAD (137.6 mg, 0.80 mmol, 5 equiv) was added with stirring until dissolution occurs. The methyl 4-hydroxyphenoxyacetate (**3**) (145.7 mg, 0.80 mmol, 5 equiv) was added, and the reaction mixture was stirred until complete dissolution was achieved. Then, neat Bu_3P (0.20 mL, 0.80 mmol, 5 equiv) was added via syringe. The mixture was stirred overnight at room temperature, after which the resin was filtered, washed with THF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL), and finally dried under high vacuum. Resin **10** (0.16 mmol) was suspended in anhydrous THF (4 mL), and $KOSiMe_3$ (102.6 mg, 0.80 mmol, 5 equiv) was added. The mixture was stirred for 24 h under a nitrogen atmosphere. After filtration, the resin was washed with THF/AcOH (2:1) (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried under high vacuum. A solution of imine **7aa** (0.80 mmol, 5 equiv) in anhydrous chloroform and triethylamine (0.13 mL, 0.96 mmol, 6 equiv) was added to a suspension of the resin-bound carboxylic acid (**11**) in anhydrous chloroform under a nitrogen atmosphere. After a few minutes, Mukaiyama's reagent (**6**) (122.6 mg, 0.48 mmol, 3 equiv) was added, and the suspension was refluxed for 2 h, after which the resin was filtered, washed with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (1 × 5 mL), and dried in vacuo. The resulting resin was subjected once more to the same reaction conditions. To release the product from the solid-phase support, the solid-supported β-lactam (**12aa**) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and washed, and the combined filtrates were evaporated under reduced pressure. The crude material was purified by column chromatography to give 19.2 mg of 1-benzyl-3-(4-hydroxy-phenoxy)-4-phenyl-azetidin-2-one (**9aa**) (50% overall yield, based on the initial loading level of the Wang resin).

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