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Report

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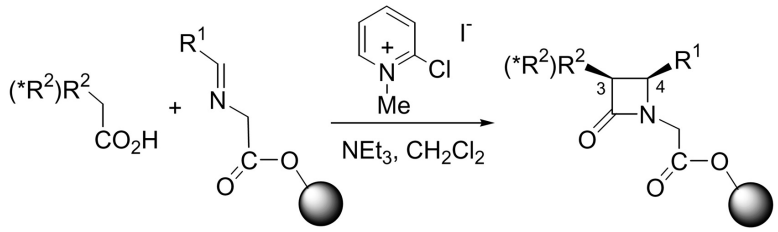

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An Efficient, Stereoselective Solid-Phase Synthesis of β-Lactams Using Mukaiyama's Salt for the Staudinger Reaction

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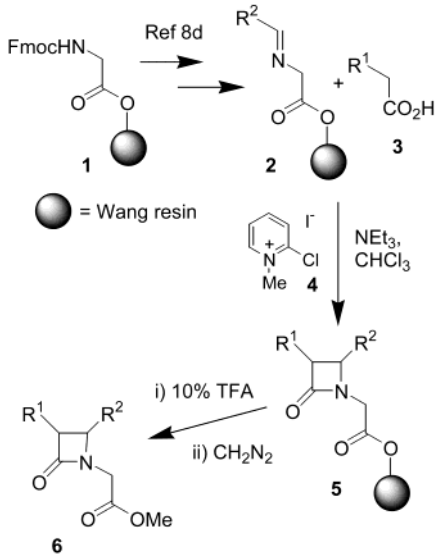
Combinatorial synthesis of small organic molecules using solid-phase approaches has evolved in the past few years to become the most powerful tool for the rapid development of novel lead compounds and for the optimization of therapeutic efficacy.[1] Undoubtedly, there is a growing need to expand the scope of solid-phase organic synthesis.

The β-lactam skeleton is the structural element of the widely used penicillins, cephalosporins, thienamycins, and other monocyclic β-lactam antibiotics,[2] such as monobactams. The constant need for new antibiotics to combat the rapid emergence of bacterial strains' resistance to traditional drugs has maintained and even increased the interest in the chemistry of β-lactams. In addition, the new application of β-lactam derivatives as inhibitors of prostate-specific antigen,[3] thrombin,[4] human cytomegalovirus protein,[5] human leukocyte elastase,[6] and cholesterol absorption[7] is another reason for the increasing interest in these kinds of compounds.

The importance of the application of solid-phase synthesis to β-lactams has been recognized by us[8] and others.[9] The favorite synthetic approach to β-lactams has been the Staudinger reaction,[10] which is a [2 + 2] cycloaddition between ketenes and imines. Acid chlorides are mostly used as precursors of ketenes in solution phase, and they have been reported for polymer-supported Staudinger reaction.[8d,9a] However, acid chlorides are sometimes unstable or difficult to prepare. This is particularly important for the development of combinatorial libraries in which easy-to-handle reagents facilitate manual parallel synthesis and require less sophisticated equipment. Various acid-activating agents have been applied to the generation of ketenes for the Staudinger reaction in solution-phase chemistry. Among them, Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) has been one of the most successful;[11] however, its application to solid-phase synthesis has not been yet reported.

As a continuation of our research on the solid-phase synthesis of biologically interesting β-lactam compounds toward the development of combinatorial libraries,[8] we decided to investigate the use of 2-chloro-1-methylpyridinium iodide as a key reagent for the construction of the β-lactam ring in a stereoselective manner.

Scheme 1



To test the reaction, cycloaddition between resin-bound aldimine **2a** (R^2 = 4-MeOPh) and phenoxylacetic acid **3a** (R^1 = PhO) was carried out (Scheme 1). Best results were obtained when 2.5 equiv of the acid and 6 equiv of triethylamine were added to a suspension of the imine in chloroform, followed by 3 equiv of 2-chloro-1-methylpyridinium iodide (**4**) and stirring at reflux temperature for 2 h. After cleavage and esterification, β-lactam **6aa** was obtained in an overall yield of 69% (Table 1, entry 1).[12] Yield decreased when more equivalents of reagents were used or an inverse addition[13,14] was attempted.

Although Staudinger reaction has been studied extensively, the precise mechanism is still unclear. The most popular explanation involves the reaction of ketene **B** with the imine to form a zwitterionic intermediate **D** (Scheme 2). Alternatively, it is the activated acid **A** that acylates the imine to form the zwitterion **D** after a proton abstraction by the base. In any case, this intermediate undergoes a conrotatory ring closing to generate the thermodynamically less stable *cis*-β-lactam **5**. However, high sterical congestion and temperature can often lead to a mixture of *cis*- and *trans*-β-lactam.

Upon applying the above conditions, the reaction of different aldimines with different carboxylic acid was accomplished (Table 1, entries 1−8). Good to high isolated yields were obtained, with some improvement over the reported yields, particularly for the *N*-phthaloylglycine (entries 5 and 7). However, mixtures of *cis*- and *trans*-β-lactams were found in some cases, particularly when the 2-furyl imine was used (entries 4 and 8).[15]

Bearing in mind our purpose of developing solid-phase chemistry that can be applied to parallel synthesis using low-budget equipment, we carried out the reaction at room temperature for 24 h. As expected, lower temperatures led

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Table 1. Solid-Phase Synthesis of β-Lactams Using 2-Chloro-1-methylpyridinium Iodide (**4**) as Acid Activating Agent

entry	β-lactam	R^1	R^2	conditions[a]	cis/trans ratio[b]	yield (%)[c,d]
1	**6aa**	PhO	4-MeOPh	A	cis	69 (68)
2	**6ab**	PhO	Ph	A	cis	85
3	**6ac**	PhO	3,4-$(MeO)_2$Ph	A	cis	68 (78)
4	**6ad**	PhO	2-furyl	A	1:3	47 (48)
5	**6ba**	phthaloyl	4-MeOPh	A	25:1	71 (38)
6	**6bb**	phthaloyl	Ph	A	17:1	74
7	**6bc**	phthaloyl	3,4-$(MeO)_2$Ph	A	cis	69 (45)
8	**6bd**	phthaloyl	2-furyl	A	2.5:1	55 (53)
9	**6ac**	PhO	3,4-$(MeO)_2$Ph	B	cis	74 (78)
10	**6ad**	PhO	2-furyl	B	cis	42 (48)
11	**6bb**	phthaloyl	Ph	B	20:1	72
12	**6bc**	phthaloyl	3,4-$(MeO)_2$Ph	B	cis	65 (45)
13	**6bd**	phthaloyl	2-furyl	B	8:1	48 (53)
14	**6ca**	CH_2=CH[e]	4-MeOPh	A	1:1.5	40
15	**6ca**	CH_2=CH[e]	4-MeOPh	C	1:1.8	64
16	**6cb**	CH_2=CH[e]	Ph	C	1:2	60

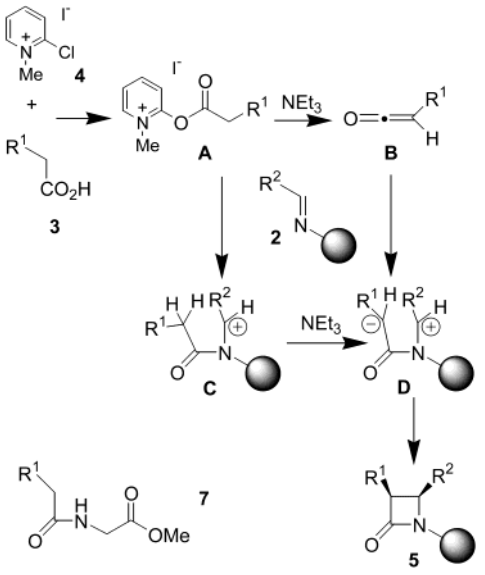
[a] A: reflux, 2 h. B: rt, 24 h. C: method A was repeated twice. [b] Determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures prior to purification. [c] Overall isolated yield after flash column chromatography of the methyl ester (**6**) (based on the initial loading level of Fmoc-Gly−Wang resin (**1**), five reaction steps). [d] Data in parentheses are reported yields; see ref 8d. [e] In these cases, the starting acid **3** was crotonic acid.

Table 2. Asymmetric Solid-Phase Synthesis of β-Lactams Using 2-Chloro-1-methylpyridinium Iodide (**4**) as Acid Activating Agent

entry	β-lactam	R^2	conditions[a]	cis/trans ratio[b]	yield (%)[c,d]
1	**10a**	4-MeOPh	A	cis	75 (78)
2	**10d**	2-furyl	A	3:1	70 (46)
3	**10a**	4-MeOPh	B	cis	77 (78)
4	**10b**	Ph	B	cis	79
5	**10c**	3,4-$(MeO)_2$Ph	B	cis	83 (45)
6	**10d**	2-furyl	B	cis	59 (46)
7	**10e**	(*E*)-Ph-CH=CH	B	cis	42 (36)

[a] A: reflux, 2 h. B: rt, 24 h. [b] Determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures prior to purification. Other stereoisomers were not detected. [c] Overall isolated yield after flash column chromatography of the methyl ester (**10**) (based on the initial loading level of Fmoc-Gly−Wang resin (**1**), five reaction steps). [d] Data in brackets are reported yields; see ref 8d.

Scheme 2



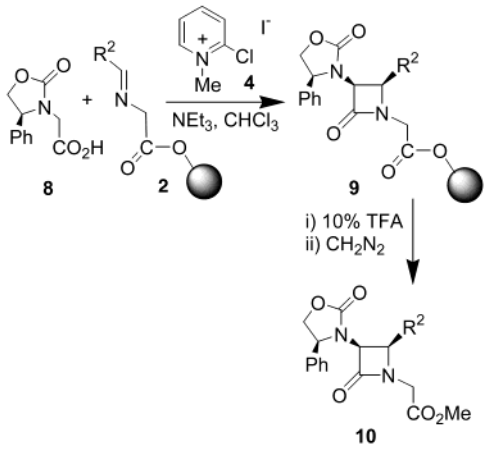
to products with better cis selectivity without decreasing the overall yield (entries 9−13).

Particularly interesting is the synthesis of α-vinyl-β-lactams that became important targets after the discovery of the carbapenem antibiotics containing alkyl, hydroxyalkyl, or acetyl at the α position of the β-lactam carbonyl.[16] Mukaiyama's activated Staudinger reaction between crotonic acid and the corresponding imine effectively gave, after refluxing for 2 h, the α-vinyl-β-lactam **6ca** in 40% yield and 1:1.5 cis/trans ratio (entry 14). This result contrasts with our previous observation that similar solid-supported Staudinger reactions using crotonyl chloride gave no detectable product. Crude product analysis of **6ca** showed that this reaction was incomplete and that some imine had survived the cycloaddition. Thus, a clear improvement in yields was achieved when a second cycle of reagent addition and 2-h reflux was attempted (entries 15 and 16).

Asymmetric synthesis on solid support is crucial for the generation of combinatorial libraries of novel optically active carbacephems and other multicyclic β-lactam derivatives.[17] Consequently, we decided to explore the solid-phase Staudinger reaction of the homochiral 4-phenyloxazolidinylacetic acid **8**[18] with several aldimines **3**, using 2-chloro-1-methylpyridinium iodide (**4**) as activating agent (Scheme 3).

The β-lactams **10** were obtained in very high overall isolated yields for the five reaction steps (Table 2). Diastereoselectivity was also very high, detecting only one diastereoisomer in all cases, with the exception of **10d** (R^2 = 2-furyl), when 2 h of reflux conditions was used (entry 2). As can be seen from Table 2, comparison to earlier research indicates that the combination of oxazolidinylacetic acid **8** and Mukaiyama's reagent is a better alternative to the

Scheme 3



corresponding acid chloride for the generation of libraries by parallel solid-phase synthesis in terms of yields and practicability, since the starting carboxylic acid can be easily handled and stored.

In summary, we have described here a methodology that provides an important series of β-lactam intermediates in a concise and practical way that facilitates the development of solid-phase libraries of biologically interesting β-lactam compounds, particularly for less equipped laboratories. Moreover, it is expected that other important targets, such as nonproteinogenic amino acids,[19] could also be efficiently generated by this route. Application of this approach to the generation of libraries of mono- and multicyclic β-lactams is currently underway.

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Supporting Information Available. General experimental procedure, spectroscopic data for all new compounds: **6bb**, **10b**, *trans*-**6ca**, *cis*-**6ca, and** *trans*-**6cb**, and ^{1}H NMR spectra of the mixture of *cis*- and *trans*-**6ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for full details.

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