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Tetrahedron Letters 45 (2004) 4085–4088
Tetrahedron Letters

Efficient and selective solid-phase synthesis of *trans* 3-alkyl β-lactams from nonactivated acid chlorides

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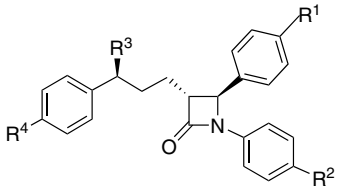
Received 9 March 2004; revised 22 March 2004; accepted 24 March 2004

Abstract—An efficient and stereoselective procedure for a rapid access to diverse *trans* 3-alkyl β-lactams by solid-phase methodology is described.

1. Introduction

Combinatorial chemistry and related parallel synthesis techniques have emerged as important tools for the discovery and development of new drugs, catalysts and materials.[1] In particular, solid-phase organic synthesis (SPOS)[2] has gained widespread acceptance in combinatorial chemistry related to drug discovery in order to accelerate lead generation and lead optimization. SPOS offers distinct advantages over solution phase chemistry: (i) filtration can be used for rapid purification; (ii) excess reagents can be used so the reactions can be driven to completion; (iii) automation is easily accomplished; and (iv) relative site isolation is achieved getting the 'pseudo-dilution effect'.[3]

On the other hand, the presence of the β-lactam skeleton (azetidin-2-one) in several widely used families of antibiotics, such as penicillins, cephalosporins, carbapenems, carbacephems and monobactams[4] has stimulated considerable research efforts towards stereoselective routes for the synthesis of this important building block. Moreover, β-lactams have been recently shown to possess biological activities as inhibitors of prostate specific antigen,[5] thrombin,[6] human cytomegalovirus protein,[7] human leukocyte elastase[8] and cysteine protease[9] and, probably the most promising discovery, azetidinones such as **1**–**2** (Fig. 1) have been described as potent cholesterol absorption inhibitors (CAI)[10] for the treatment of hypercholesterolemia.



1 Sch 48461 R^1&R^2=OMe, R^3&R^4=H
2 Sch 58235 R^1&R^3=OH, R^2&R^4=F

Figure 1.

We were interested in the application of solid-phase chemistry to the preparation of 3-alkyl β-lactams, which would be the starting point for the production of libraries of compounds for biological screening.

The most popular method for the preparation of the β-lactam ring involves the classical ketene–imine (Staudinger) reaction, that has been extensively used in the preparation of β-lactams both in solution and solid-phase chemistry.[11] In most of the cases, acid chlorides are employed for the in situ generation of the ketene and these acid chlorides are activated with nitrogen, oxygen, sulfur, aryl or alkenyl at the α-position to give preferentially *cis* selectivity. In contrast, there have been only few examples of the use of nonactivated aliphatic acid chlorides in the homogeneous β-lactam synthesis, often with low yield and selectivity,[12] and the corresponding solid-phase synthesis has not yet been reported.

Keywords: Azetidiones; Solid-phase synthesis; Staudinger reaction; Cholesterol absorption inhibitors.
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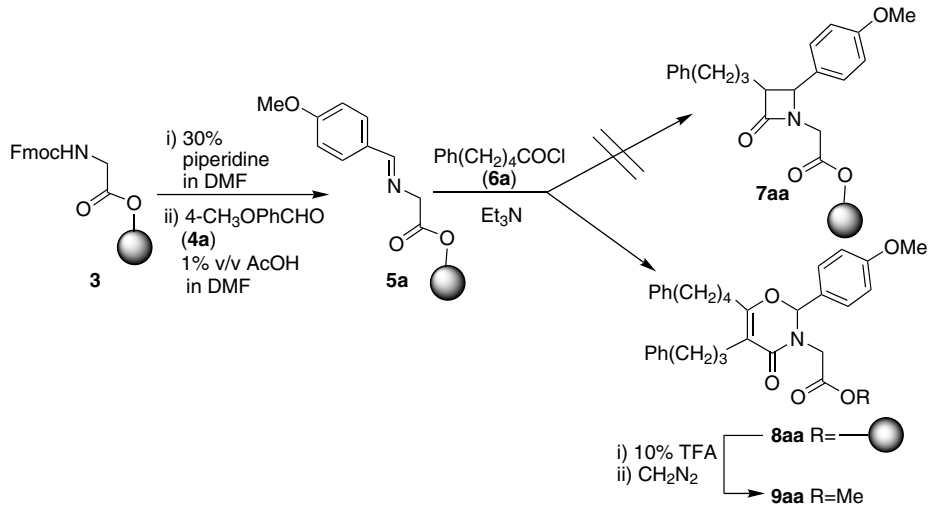
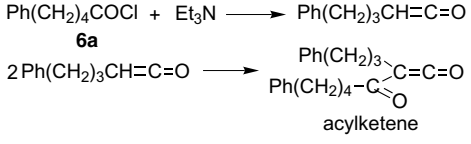
doi:10.1016/j.tetlet.2004.03.145



Scheme 1.

In order to develop a strategy for the solid-phase of 3-alkyl β-lactams, we decided to carry out the synthetic sequence starting from Fmoc-glycine tethered to Wang resin (**3**) (Scheme 1). The amine group was deprotected by treatment with 30% piperidine in DMF and condensed with *p*-anisaldehyde (**4a**) in 1% acetic acid in DMF to give the aldimine **5a**. The subsequent [2 + 2] cycloaddition between the in situ generated ketene and imine **5a**, was attempted by adding an excess of 5-phenylvaleroyl chloride (**6a**) (15 equiv) and triethylamine (20 equiv) to a dichloromethane suspension of imine **5a**, at room temperature for 12 h. However, this reaction failed to give the desired resin bound β-lactam **7aa**. In contrast, a non-β-lactamic product was obtained; after resin cleavage with 10% trifluoroacetic acid in dichloromethane followed by esterification with diazomethane, this compound was identified as the oxazinone **9aa** (40%, overall isolated yield, based on manufacturer's loading of Fmoc-Gly-Wang resin).

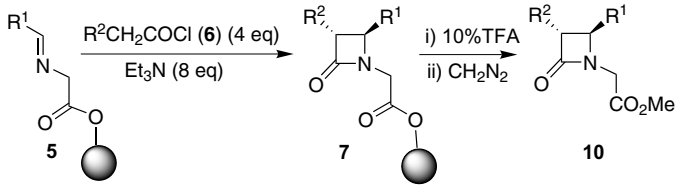
This unusual reaction is mainly due to the propensity of ketenes to dimerization to form acylketenes (Scheme 2). The excess of the alkanoyl chloride favoured the formation of the acylketene. The acylketenes are known to be highly reactive and show a pronounced tendency to undergo regioselective [2 + 4] Diels–Alder reactions with electron-rich and/or dipolar dienophiles.[13] Thus, the acylketene reacts with the imine **5a** to perform the oxazinone **9aa**.



Scheme 2.

In order to avoid formation of **9aa**, the reaction was performed using 2 equiv of **6a** and 4 equiv of triethylamine in refluxing toluene. However, after resin cleavage and esterification, detached β-lactam **10aa** (R^1 = 4-MeOPh, $R^2 = Ph(CH_2)_3$) was isolated in low yield together with aldehyde **4a**, indicating an incomplete conversion. Finally, optimized conditions were achieved by adding a controlled excess of **6a** (4 equiv) and triethylamine (8 equiv) to the resin bound imine **5a** in refluxing toluene for 12 h. Following resin cleavage and esterification, β-lactam **10aa** was obtained as a single product with excellent *trans* [14] selectivity, in a 57% overall isolated yield (based on manufacturer's loading of Fmoc-Gly-Wang resin) (Scheme 3).

After the solid-phase synthesis of the prototypical β-lactam **10aa**, the procedure was successfully extended to different 3-alkyl β-lactam and the results are listed in Table 1. Good to high overall yields of β-lactams were obtained and only the *trans* isomers were isolated. R^1 can be aryl substituted with electron donating or withdrawing groups. R^2 includes the 3-phenylpropyl side chain (entries 1–4), present in potent cholesterol absorption inhibitor Sch 48461. When running the reaction with stable, distilled acid chlorides (entries 5–9),



Scheme 3.

Table 1. Solid-phase synthesis of *trans* 3-alkyl β-lactams

Entry	β-Lactam	R^1	R^2	Conditions	Yield (%)[a]
1	**10aa**	4-MeOPh	$Ph(CH_2)_3$[b]	4 equiv R^2CH_2COCl, 8 equiv NEt_3	57
2	**10ba**	Ph	$Ph(CH_2)_3$[b]	4 equiv R^2CH_2COCl, 8 equiv NEt_3	57
3	**10ca**	CH_3-Ph	$Ph(CH_2)_3$[b]	4 equiv R^2CH_2COCl, 8 equiv NEt_3	56
4	**10da**	4-BrPh	$Ph(CH_2)_3$[b]	4 equiv R^2CH_2COCl, 8 equiv NEt_3	43
5	**10ab**	4-MeOPh	CH_3[c]	3 equiv R^2CH_2COCl, 6 equiv NEt_3	52
6	**10cb**	CH_3-Ph	CH_3[c]	3 equiv R^2CH_2COCl, 6 equiv NEt_3	54
7	**10ac**	4-MeOPh	CH_3CH_2[c]	3 equiv R^2CH_2COCl, 6 equiv NEt_3	51
8	**10ad**	4-MeOPh	$CH_3CH_2CH_2CH_2$[c]	3 equiv R^2CH_2COCl, 6 equiv NEt_3	48
9	**10dd**	4-BrPh	$CH_3CH_2CH_2CH_2$[c]	3 equiv R^2CH_2COCl, 6 equiv NEt_3	50

[a] Overall isolated yield after flash column chromatography of the methyl ester (**10**) [based on the initial loading level of Fmoc-Gly-Wang resin (**3**), five reaction steps].
[b] Prepared in situ from the corresponding carboxylic acid and oxalyl chloride.
[c] From the corresponding distilled acid chloride.

we found that the use of 3 equiv was optimum, while for an in situ generated acid chloride (entries 1–4) 4 equiv gave the best results.

In conclusion, to the best of our knowledge, this is the first example of the solid-phase preparation of *trans* 3-alkyl β-lactams. The efficient and stereoselective protocol described here could be quite useful for the rapid generation of libraries of these biologically interesting compounds. We have found conditions for the successful polymer-supported Staudinger reaction using a controlled excess of the nonactivated acid chloride and the tertiary amine.

2. Typical procedure

Preparation of **7aa**. 5-Phenylvaleric acid (0.053 g, 0.3 mmol, 4 equiv) and oxalyl chloride (0.040 mL, 0.45 mmol) were stirred in anhydrous dichloromethane (1.9 mL) for 3 h, after that the mixture was evaporated in vacuo to give the crude 5-phenylvaleroyl chloride (**6a**), which was used without further purification. To a suspension of resin bound imine **5a** (0.086 g, 0.075 mmol, 0.87 mmol/g) in dry toluene (2.2 mL) was added dropwise triethylamine (0.084 mL, 0.6 mmol, 8 equiv) and the solution of crude 5-phenylvaleroyl chloride (**6a**) (4 equiv) in toluene (0.8 mL). The reaction mixture was stirred at reflux overnight. The resin was washed with CH_2Cl_2 (3×2 mL), AcOEt (3×2 mL), MeOH (3×2 mL) and CH_2Cl_2 (2 mL) and finally drying in vacuo overnight to afford resin **7aa**. *Preparation of* **10aa**. A suspension of resin bound β-lactam **7aa** (0.097 g, 0.073 mmol, 0.75 mmol/g) in 10% TFA in CH_2Cl_2 (3 mL) was stirred at room temperature for 50 min. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL) and treated with a diazomethane solution in ether at 0 °C. After methylation was completed, solvent was evaporated and the crude product was subjected to flash chromatography using hexane–ethyl acetate (70:30) to give **10aa** (15.3 mg, 57%).[15]

Acknowledgements

Financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Tecnológica, Fundación Antorchas and Universidad Nacional de Rosario from Argentina and Royal Society of Chemistry (UK) is gratefully acknowledged. C.M.L.D. thanks CONICET for fellowship. We also thank Lic. G. De Benedetti and M. E. Vallet (Dow Química Argentina) for the IR spectra.

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14. The assignment of the *trans*-stereochemistry to β-lactams was based on the observed coupling constants of about 2.0 Hz for methine protons H-3 and H-4 in the ^{1}H NMR spectra.
15. *Data of representative products*: Compound **10aa**: IR (film) 1768 (β-lactam), 1747 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60–1.95 (m, 4H), 2.62 (t, $J = 6.8$ Hz, 2H), 3.05 (br t, $J = 5.6$ Hz, 1H), 3.40 (d, $J = 18$ Hz, 1H), 3.68 (s, 3H), 3.80 (s, 3H), 4.31 (d, $J = 18$ Hz, 1H), 4.45 (d, $J = 2$ Hz, 1H), 6.87–7.26 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.00, 28.80, 35.60, 40.90, 52.10, 55.23, 61.00, 61.32, 114.36, 125.71, 127.64, 128.22, 128.27, 129.18, 141.73, 159.77, 168.59, 170.77. Anal. HRMS Calcd for $C_{22}H_{25}NO_4$ (M^+, m/z): 367.1784. Found: 367.1796. Compound **10cb**: IR (film) 1775 (β-lactam), 1754 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (d, $J = 7.3$ Hz, 3H), 2.36 (s, 3H), 3.02–3.14 (dq, $J = 2$ and 7.3 Hz, 1H), 3.43 (d, $J = 18$ Hz, 1H), 3.71 (s, 3H), 4.35 (d, $J = 18$ Hz, 1H), 4.41 (d, $J = 2$ Hz, 1H), 7.19 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.67, 21.00, 41.01, 52.10, 55.84, 63.10, 126.29, 129.56, 134.27, 138.36, 168.58, 171.39. Anal. HRMS Calcd for $C_{14}H_{17}NO_3$ (M^+, m/z): 247.1208. Found: 247.1207. Compound **10ac**: IR (film) 1773 (β-lactam), 1754 (ester) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, $J = 7.4$ Hz, 3H), 1.79–2.00 (m, 2H), 3.01 (ddd, $J = 2$, 6.2, 8.2 Hz, 1H), 3.41 (d, $J = 18$ Hz, 1H), 3.71 (s, 3H), 3.81 (s, 3H), 4.34 (d, $J = 18$ Hz, 1H), 4.49 (d, $J = 2$ Hz, 1H), 6.91 (d, $J = 8.6$ Hz, 2H) 7.23 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.27, 21.44, 40.81, 52.11, 55.23, 60.77, 62.52, 114.31, 127.60, 129.40, 159.69, 168.66, 170.79. Anal. HRMS Calcd for $C_{16}H_{20}BrNO_3$ (M^+, m/z): 277.1314. Found: 277.1307.