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Solid-Phase Synthesis of β-Lactams via the Ester Enolate–Imine Condensation Route

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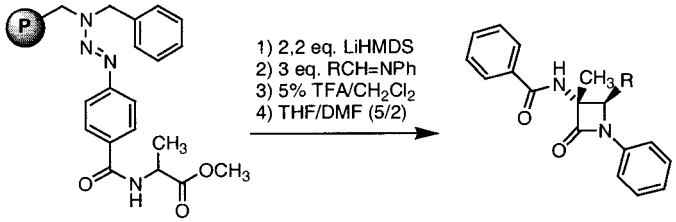
ABSTRACT



The ester enolate–imine condensation route to β-lactams via an immobilized ester enolate has been achieved for the first time. The key reaction in the synthesis is the cyclization of the resin bound ester dianion and an imine. Traceless cleavage from the T1-triazene linker system yields the desired β-lactams.

β-Lactam-based antibiotics include penicillins, cephalosporins, carbapenems, norcardins, and monobactams.[1] These compounds constitute a large class of broad-spectrum antibiotics that effectively combat bacterial infections. Solid-phase organic synthesis enables the preparation of large numbers of structurally related molecules in short periods of time, which is especially important for the optimization of lead structures in the pharmaceutical industry. Despite these facts, the solid-phase synthesis of β-lactams has not been widely reported.[2]

The first preparation of a β-lactam was reported in 1907, when Staudinger described the cycloaddition between ketenes and imines.[3] The Staudinger reaction has been immobilized by Ruhland et al. in 1996.[2a] In 1943 Gilman and Speeter developed a one-pot ester−imine condensation to yield β-lactams.[4] Since this initial report, several research groups have investigated the reaction and established the condensation of ester enolates with imines as an important synthetic methodology for the preparation of β-lactams.[5] We now report, to the best of our knowledge, the first ester enolate−imine condensation route to β-lactams employing an immobilized ester enolate.

The main reasons for choosing the T1-triazene linker system[6] to immobilize the ester were its stability in basic

(1) (a) Manhas, M. S.; Bose, A. K. *β-Lactams: Natural and Synthetic*; Wiley: New York, 1971, Part 1. (b) Lednicer, D. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1995; Vol. 5.

(2) For solid-phase synthesis, see: (a) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253−254. (b) Pei, Y.; Houghten, R. A.; Kiely, J. S. *Tetrahedon Lett.* **1997**, *38*, 3349−3352. (c) Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820−7826. (d) Singh, R.; Nuss, J. M. *Tetrahedon Lett.* **1999**, *40*, 1249−1252. For soluble-polymer-supported synthesis, see: (e) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem. Eur. J.* **2000**, *6*, 133−138. (f) Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedon Lett.* **1999**, *40*, 2019−2020. (g) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedon Lett.* **1998**, *39*, 1257−1260. For the attatchment of preformed β-lactams to various polymers, see: (h) Furman, B.; Thürmer, R.; Kałuza, Z.; Voelter, W.; Chmielewski, M. *Tetrahedon Lett.* **1999**, *40*, 5909−5912. (i) Furman, B.; Thürmer, R.; Kałuza, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem.* **1999**, *111*, 1193−1195; *Angew. Chem., Int. Ed.* **1999**, *38*, 1121−1123. (j) Matta, E. G. *Tetrahedon Lett.* **1997**, *38*, 6335−6338.

(3) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51−123.

(4) Gilman, H.; Speeter, H. J. *J. Am. Chem. Soc.* **1943**, *65*, 2255−2256.

(5) For reviews, see: (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447−1465. (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225−2244. (c) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 4.1, pp 893−951.

(6) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem.* **1998**, *110*, 3614−3616; *Angew. Chem., Int. Ed.* **1998**, *37*, 3413−3415.

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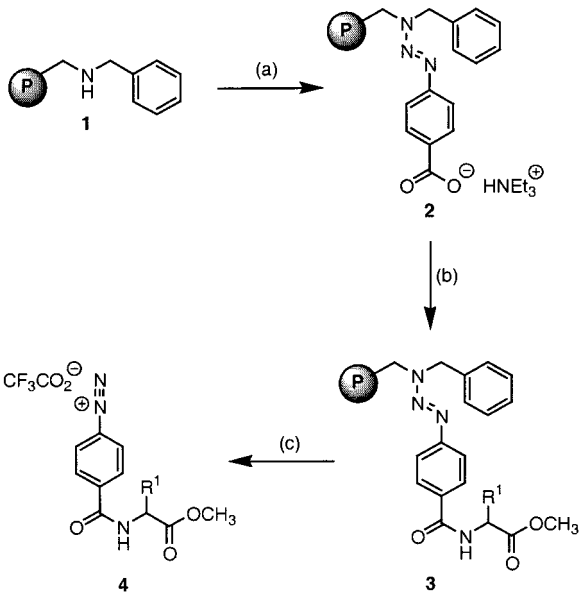
Scheme 1[a]



[a] (a) 1. 5 equiv of *p*-aminobenzoic acid, 10 equiv of $BF_3 \cdot Et_2O$, 10 equiv of ^{t}BuONO, THF, −10 °C, 1 h; 2. **1**, pyridine/DMF (1:1), rt, 1 h; (b) **2**, 3 equiv of amino acid methyl ester·HCl, 2 equiv of 2-chloro-1-methylpyridinium iodide, 20 equiv of NEt_3, CH_2Cl_2, rt, 12 h; (c) 5% TFA/CH_2Cl_2.

media and the possibility of introducing a variety of functionalities by applying different cleavage procedures.[7]

A simple three-step procedure (Scheme 1) starting from benzylamine resin **1** via **2** gave ester resins **3** with high loading and excellent purity of the corresponding cleavage products **4** (Table 1).

Table 1. Preparation of Ester Resins **3** and Diazonium Salts **4**

3, **4**	R^1	loading (**3**)[a]	purity (**4**)[b]
a	H	94%	≥96%
b	Me	97%	95%
c	Ph	98%	94%

[a] Resins identified by IR spectroscopy. Loading of resins **3** determined by nitrogen elemental analysis. [b] Purity of diazonium salts **4** determined by ^{1}H NMR spectroscopy (solvent: d_4-MeOH).

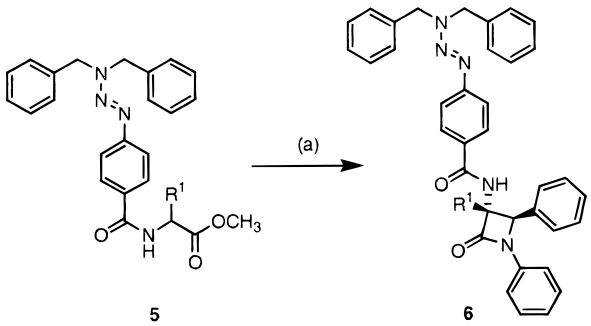
Treatment of **1** with 4-carboxybenzenediazonium tetrafluoroborate yielded T1-benzoic acid resin **2**. This reaction has to proceed under basic conditions, but only pyridine and lutidine were found to be reasonable bases. Other bases, e.g., triethylamine, Hünig's base, DMAP, and ^{t}BuOK, resulted in decomposition of the diazonium salt. Standard conditions are applied for the diazotation of *p*-aminobenzoic acid with *tert*-butyl nitrite.[8]

Several peptide-coupling reagents (e.g., 2-chloro-1-methylpyridinium iodide, *N*-ethyl-*N*′-[3-(dimethylamino)propyl]-carbodiimid hydrochloride/1-hydroxybenzotriazol (EDC/HOBt), and pentafluorophenyl diphenylphosphinate (FDPP)) were tested in the synthesis of resins **3** (step b). Since all coupling reagents gave the same results, 2-chloro-1-methylpyridinium iodide was used for convenience. Resin **3b** affords diazonium salt **4b** after treatment with 5% TFA/CH_2Cl_2. To obtain pure cleavage products **4**, the triazene formation reaction (step a) had to be carried out at room temperature. Lower temperatures resulted in lower purity of **4** and lower loading of **3** (e.g., triazene formation at −10 °C, 1 h ⇒ purity = 75%, loading = ∼80%).

Table 1 shows the results for the reaction sequence **1** → **4** (Scheme 1) with different α-substituted amino acid methyl esters. The loading of resins **3a**−**3c** and the purity of the different diazonium salts **4a**−**4c** were very good.[9]

The ester enolate−imine condensation was initially tested in the liquid phase (Scheme 2) on model compound **5b**. This

Scheme 2[a]



[a] (a) 1. 2.2 equiv of LiHMDS, THF, −78 °C, 20 min; 2. 1 equiv of PhCH=NPh, −78 °C to rt, 23 h; 3. H_2O.

reaction gave *β*-lactam **6b** in 71% yield and de ≥ 96%.[10] The relative configuration of **6b** was determined by NOE experiments to be *trans*. The cyclization reaction with compound **5a** afforded, not surprisingly, only complex product mixtures which were not further investigated.[11] LiHMDS was found to give best results for dianion generation.

(7) (a) Bräse, S.; Schroen, M. *Angew. Chem.* **1999**, *111*, 1139−1142; *Angew. Chem., Int. Ed.* **1999**, *38*, 1071−1073. (b) Bräse, S.; Dahmen, S. In press.

(8) Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1999**, 1357−1366.

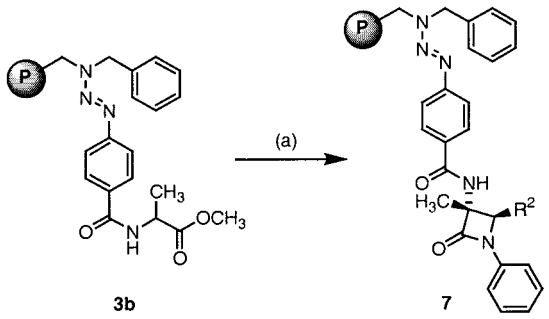
(9) **Typical procedure:** All reactions were carried out in absolute solvents under an argon atmosphere. *p*-Aminobenzoic acid (16 mmol) was dissolved in 50 mL of THF and cooled to −10 °C; $BF_3 \cdot Et_2O$ (32 mmol) and *tert*-butyl nitrite (32 mmol) were added. The reaction mixture was stirred at −10 °C for 1 h and then diluted with 25 mL of pyridine and 25 mL of DMF. Benzylamine resin **1** (3.2 mmol) was added and the resulting mixture stirred at rt for 1 h. The resin was washed with pyridine/DMF, THF/NEt_3, and MeOH/NEt_3. Resin **2** (3.2 mmol) and 2-chloro-1-methylpyridinium iodide (6.4 mmol) were suspended in 80 mL of CH_2Cl_2, before 20 equiv of NEt_3 was added. Alanine methyl ester hydrochloride (9.6 mmol) was added after 15 min. The resulting mixture was stirred overnight at rt. The resin was washed with THF, Et_2O, and MeOH. Resin **3** was collected in a glass pipet and suspended in 5% TFA/CH_2Cl_2. The acidic solution was filtered from the resin after 1 min. This procedure was repeated three times to yield **4**.

(10) Reaction conditions were not optimized.

(11) Low yields of α-unsubstituted esters in ester enolate−imine condensation reactions have been described in the literature, see e.g., ref 5a.

The liquid-phase reaction conditions were transferred to the solid phase (Scheme 3) without any problems.[12] It is most

Scheme 3[a]

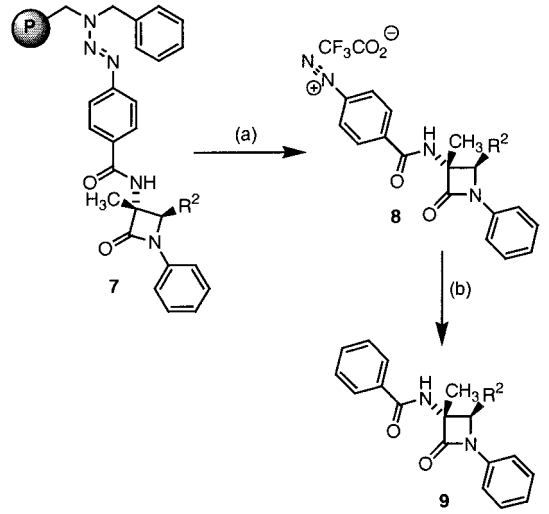


[a] (a) 1. 2,2 equiv of LiHMDS, THF, −78 °C, 1,5 h; 2. 3 equiv of $R^2CH{=}NPh$, −78 °C to rt, 23 h; 3. H_2O.

probable that the reaction proceeds, as in liquid phase, via a dianion.[13]

The condensation reaction of **3b** was carried out with a range of imines, which all gave very good results concerning loading of the lactam resin **7** and purity of the cleaved diazonium salt **8** (Scheme 4).

Scheme 4[a]



[a] (a) 5% TFA/CH_2Cl_2; (b) THF/DMF (5/2), 60 °C, 15 min.

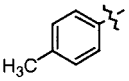
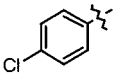
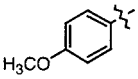
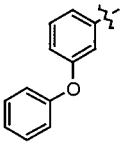
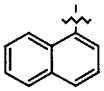
The diazonium salts were reasonably stable at room temperature and could be analyzed by ^{1}H NMR spectroscopy in d_4-MeOH.

Several procedures to transform the diazonium salts into traceless products had to be tested before formation of pure β-lactams could be achieved. All methods were first tested on resin **3a** and then further optimized on resin **7a**. Conditions published to date[6] for traceless cleavage from a T1-triazene linker resulted in decomposition of the sensitive β-lactams.

During the investigations on diazonium salts, we found out that they can easily be transformed into deuteriomethoxy-substituted products.[14] Surprisingly, changing d_4-MeOH to MeOH does not yield the methoxy-substituted products but instead traceless products. To yield methoxy-substituted products, reaction conditions had to be altered from d_4-MeOH, rt, 48 h to MeOH, 5% TFA, 60 °C, 30 min. Traceless cleavage with methanol could not be applied to a wide range of resins, because in most cases products were mixtures of methoxy and traceless compounds.[15] Since these mixtures could only be purified by column chromatography, we decided to investigate other methods.

The best conditions for traceless cleavage turned out to be modified Keumi[16] conditions (2-fluorenediazonium tetrafluoroborate, 1,2 equiv of chlorotrimethylsilane, THF/DMF (5/3), 60 °C, 60 min). Optimized conditions for diazonium salt **4a** were THF/DMF (5/2), rt, 12 h. These conditions, applied to diazonium salt **8a**, lead to the formation of intensely colored side products. Changing reaction conditions to THF/DMF (5/2), 60 °C, 15 min gave the best results for lactam resins and very good results for resins **4**. Purity of traceless compounds by GC/MS are as follows: **4a** (94%), **4b** (91%), **4c** (93%). Lactams **9** were easily separated from yellow byproducts by dissolving them in EtOAc/pentane (40:60) and eluting them through 7 cm SiO_2. Results achieved using this procedure are shown in Table 2.

Table 2. Preparation of β-Lactams **9**

9	R^2	loading (**7**) [%][a]	purity [%][b]	yield [%][c]	de [%][d]
a		96	89	54	≥ 96
b		86	93	53	≥ 96
c		95	98	54	≥ 96
d		84	94	69	≥ 96
e		97	93	71	93
f		84	90	56	50
g		97	89	69	≥ 96
h		97	88	61	90

[a] Resins identified by IR spectroscopy. Loading of resin **7** determined by nitrogen elemental analysis. [b] Compounds **9** identified by ^{1}H/^{13}C NMR spectroscopy and MS. Purity of compounds **9** determined by HPLC. [c] Yields of β-lactams **9** after six steps based on theoretical loading of Merrifield resin. [d] de determined by ^{13}C NMR spectroscopy.

Eight different β-lactams **9** were prepared in high purity, excellent diastereoselectivity, and good yields. No change in diastereomeric purity could be observed by comparing the ^{1}H NMR spectra of compounds **8** and **9**. The relative configuration of β-lactams **9c**, **9e**, **9g**, and **9h** was determined by NOE experiments to be *trans*. Assuming a uniform reaction pathway, we assign compounds **9a**−**h** as having the *trans* configuration. This is the same configuration as found in solution-phase synthesis of **9a**.[17]

In conclusion, the first solid-phase synthesis of β-lactams via ester enolate−imine condensation employing an immobilized ester enolate has been developed. The substrates were attatched to the polymer with a T1-triazene linker, which was cleaved traceless.

We are currently employing the established synthesis for the preparation of highly diverse β-lactam libraries.

Acknowledgment. We thank Dr. J. Runsink for carrying out the NOE investigations. This work was supported by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg Stipendium to S.S.) and the Fonds der Chemischen Industrie. We thank Calbiochem Novabiochem AG, Degussa-Hüls AG, BASF AG, the former Hoechst AG, Bayer AG, and Wacker Chemie for the donation of chemicals.

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(12) **Typical procedure:** LiHMDS was added to resin **7** (0, 96 mmol) in 25 mL of THF at −78 °C and the resulting mixture was stirred for 1.5 h. After addition of the imine (2.88 mmol), the reaction mixture was warmed from −78 to 0 °C within 16 h and then stirred at rt for 7 h. Lactam resin **7** was washed with THF, Et_2O, and MeOH. Resin **7** was collected in a glass pipet and suspended in 5% TFA/CH_2Cl_2. The acidic solution was filtered from the resin after 1 min. This procedure was repeated three times to yield **10**. Diazonium salt **10** obtained by cleavage from 100 mg of resin **7** was dissolved in 4 mL of THF/DMF (5/2) and heated to 60 °C for 15 min. Pure β-lactams were obtained by evaporating the solvent and elution of the crude product over 7 cm of SiO_2.

(13) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698−1701.

(14) Reaction conditions: d_4-MeOH, rt, 48 h.

(15) Broxton, T. J.; Bunnett, J. F.; Paik, C. H. *J. Org. Chem.* **1977**, *42*, 643−649.

(16) Keumi, T.; Umeda, T.; Inoue, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 89−95.

(17) Gluchowski, C.; Cooper, L.; Breigbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413−3416.