The Acid Chloride–Iminoester Condensation: a Direct Approach to PS-5 and PS-6 Intermediates and Related Compounds

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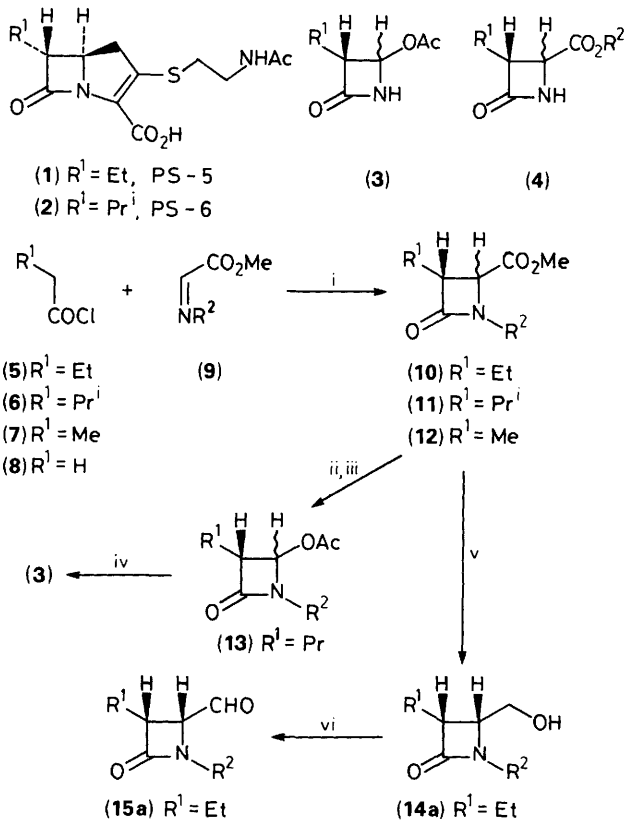
The dehydrochlorination of alkanoyl chlorides with triethylamine in the presence of α-iminoesters produced 3-alkyl-4-alkoxycarbonyl β-lactams in excellent yields and high stereoselectivity.

Antibiotics PS-5 (**1**) and PS-6 (**2**), and related systems, comprise an interesting family of streptomycete metabolites characterized by the presence of alkyl side chains adjacent to the β-lactam carbonyl.[1] Most of the reported syntheses of these compounds involve as a key step the formation of a 3-alkyl-4-acetoxyazetidin-2-one (**3**), usually generated from a preformed 4-alkoxycarbonylazetidin-2-one (**4**).[2] Also the alkoxycarbonyl group could be converted into a diverse array of functionalities leading to a variety of useful carbapenem intermediates.[3] Recently we have reported[4] a short synthesis of 3-alkyl-4-acetoxyazetidin-2-ones by using the α-bromoester–imine condensation as an approach to the azetidinone ring. Unfortunately, this approach fails when iminoesters are used as the imino components;[5] neither did the lithium enolate–iminoester condensation afford 4-alkoxycarbonyl β-lactams.[6] Among other approaches for the construction of 4-alkoxycarbonyl β-lactams,[7] the acid chloride–iminoester condensation has proved to be efficient with acid chlorides bearing electron-withdrawing substituents at the α-position.[8] However, the direct preparation of 3-alkyl-β-lactams from monoalkylketenes, generated from their corresponding acid chlorides, is often limited in scope.[9] We now report that a wide variety of 3-alkyl-4-alkoxycarbonyl β-lactams can be directly obtained by reaction between alkanoyl chlorides and iminoesters† in the presence of triethylamine, thus providing a straightforward access to a variety of carbapenem building blocks.

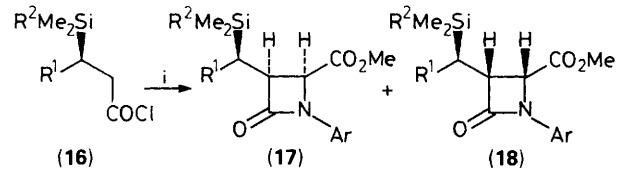


Scheme 1. *Reagents and conditions:* i, NEt_3, hexane, reflux, 12—15 h; ii, LiOH, tetrahydrofuran (THF)–H_2O, 25 °C, 1 h; iii, $Pb(OAc)_4$, AcOH, dimethylformamide (DMF), 70 °C; iv, $(NH_4)_2Ce(NO_3)_6$ (CAN), MeCN–H_2O, 0—5 °C, 30 min; v, $LiBH_4$, THF, room temp., 60 min; vi, Me_2SBr_2, CH_2Cl_2, −25 °C, 2 h, then NEt_3.

Preparation of the racemic form of the known PS-5 intermediate (**10a**) was first examined. Thus, reaction between butanoyl chloride (**5**) and the imine (**9a**) in the presence of triethylamine in a 2 : 1 : 3 ratio in refluxing hexane for 14 h afforded the expected 3-ethyl-4-methoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-one (**10a**) in 90% yield as a mixture of *cis*- and *trans*-isomers in an 83 : 17 ratio; the *cis*-isomer [δ 3.50 (m, H-3) and 4.60 (d, *J* 6 Hz, H-4)] was separated by crystallization from cyclohexane (m.p. 81—82 °C). The change of the solvent from hexane to a more polar one, like acetonitrile, caused an increase in the stereoselectivity of the reaction but the chemical yield was found to be lower than in the former case. Also, the yield of the β-lactam (**10a**) decreased to 35% when the reaction was carried out at room temperature in benzene as solvent. Similar results were obtained when isovaleryl chloride (**6**) was used instead of butanoyl chloride (**5**) to give the (±) PS-6 intermediate (**11a**) (m.p. 119—120 °C, *cis*-isomer). Similarly, the 3-methyl analogue (**12a**) (m.p. 74—76 °C, *cis*-isomer) could be obtained in 86% yield starting from propanoyl chloride (**7**). Exceptionally, in the case of acetyl chloride (**8**) we did not observe any β-lactam formation. These β-lactams thus prepared in a one-step synthesis could be further elaborated by standard methodology to furnish the corresponding 4-acetoxyazetidin-2-ones (**3**) as carbapenem building blocks.[2] For instance, the β-lactam (**10a**) upon saponification and further decarboxylation–acetoxylation[10] furnished a 28 : 72 ratio of *cis*- and *trans*-isomers of the (±) PS-5 carbapenem precursor (**13a**) in 50% overall yield. Alternatively, the *cis*-β-lactam (**10a**) was converted into the aldehyde (**15a**) [m.p. 92—94 °C; δ 4.49 (dd, *J* 3.6 and 6.1 Hz, H-4) and 9.87 (d, *J* 3.6 Hz, C*H*O)] by borohydride reduction[7a] of (**10a**)‡ and further oxidation of the resulting hydroxy compound (**14a**) (m.p. 103—104 °C) by dimethylbromosulphonium bromide–triethylamine.[11] The aldehyde (**15a**) with *cis*-stereochemistry at C(3)–C(4) of the

† Iminoesters have also been used in a novel formally [2 + 2] cycloaddition reaction with acetyl ketene presumably generated from diketene, see: M. Sunagawa, K. Goda, M. Enomoto, and A. Sasaki, *Heterocycles*, 1984, **21**, 430.

‡ Direct reduction of (**10a**) to (**15a**) by the usual procedure (*i.e.* Bu^i_2AlH) was unfruitful, probably owing to the steric constraints imposed by the 3-ethyl substituent *cis* to the alkoxycarbonyl group.



(16) (17) (18)

a; R^1 = Ph, R^2 = Me
b; R^1 = Me, R^2 = Ph

Scheme 2. *Reagents and conditions:* i, (**9a**), hexane or MeCN, reflux, 14 h (Ar = 4-$MeOC_6H_4$).

Table 1. 4-Methoxycarbonyl β-lactams (**10**)—(**12**).

Compound[a]	Solvent	Yield (%)[b]	*cis* : *trans*[c]
(**10a**)	Hexane	90	83 : 17
	Benzene	82	85 : 15
	THF[d]	48	90 : 10
	MeCN	47	94 : 6
(**10b**)	Benzene	85	100 : 0[d]
(**10c**)	Benzene	40	100 : 0[e]
(**10d**)	Benzene	90	100 : 0
(**11a**)	Hexane	88	83 : 17
	THF	60	92 : 8
(**12a**)	Hexane	86	85 : 15
	THF	48	90 : 10

[a] Products were racemic mixtures and gave satisfactory spectral and analytical data. [b] Yields based on weight of isolated product from column chromatography on silica gel. [c] Determined by 300 MHz NMR spectroscopy. [d] Obtained as a 1 : 1 mixture of diastereoisomers. [e] From the crude α-iminoester, yield not optimized. [d] Tetrahydrofuran.

β-lactam ring would be of potential interest in the synthesis of the unnatural (±)-6-*epi* PS-5 carbapenem.[12]

In order to determine the scope of the method we extended our study to glyoxalate imines (**9b**)—(**9d**) and results are summarized in Table 1. Although diastereoselection was not apparent in the case of the iminoester (**9b**) derived from methyl glyoxalate and (*R*)-α-naphthylethylamine, the following results are particularly noteworthy: first, the chemical yields and stereoselectivity are high, thus providing a convenient direct route to a variety of β-lactam intermediates amenable to further transformations; secondly, the reaction can be applied to α-iminoesters derived from aromatic and aliphatic amines involving acid- or base-sensitive functionalities, which cannot be used under standard acidic or basic enolate–imine conditions.

Other α-unactivated carboxylic acids could also be used in such acid halide–iminoester processes (Scheme 2). For instance, β-trimethylsilyl-β-phenylpropanoyl chloride (**16a**) upon treatment with the iminoester (**9a**) in hexane as solvent furnished a diastereoisomeric mixture§ of *cis*-β-lactams (**17a**) and (**18a**) as the sole products in a ratio of 30 : 70, from which the β-lactam (**18a**) could be separated by crystallization from hexane [m.p. 142—144 °C; δ 4.30 (dd, $J_{1',3}$ 13.4, $J_{3,4}$ 5.5 Hz, H-3), 4.47 (d, $J_{4,3}$ 5.5 Hz, H-4), and 2.74 (d, $J_{1',3}$ 13.4 Hz, H-1')]. Under the same conditions as above, compound (**16b**) gave a mixture of four diastereoisomers of the corresponding *cis*- and *trans*-β-lactams in a 34 : 66 ratio, respectively. As expected the proportion of the *cis*-isomers was increased when the reaction was carried out in acetonitrile as solvent giving (**18b**) [δ 3.44 (dd, $J_{1',3}$ 12.4, $J_{3,4}$ 5.6 Hz, H-3), 4.56 (d, $J_{4,3}$ 5.6 Hz, H-4), and 1.43 (dq, $J_{1',3}$ 12.4, $J_{1',2'}$ 7.2 Hz, H-1')] as the main product.¶ These results assume added significance in view of the fact that a silyl group can be easily transformed into the hydroxy function present in the antibiotic thienamycin[13] with the correct stereochemistry at the 1' and C-3 positions.

In conclusion we have demonstrated that the presently described method provides a convenient direct route to a wide variety of 3-alkyl-4-alkoxycarbonyl-β-lactams which is of interest not only for *trans*-carbapenems but also for the synthesis of β-lactams with *cis*-geometry as found in some of the olivanic acids.[1] Further studies on the application of the present method to the synthesis of optically active carbapenem compounds starting from optically active alkanoyl chlorides and glyoxalates are now underway.

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References

1 For reviews on β-lactam antibiotics, see: 'Chemistry and Biology of β-Lactam Antibiotics,' eds. R. B. Morin and M. Gorman, Academic, New York, 1982, vols. 1—3; 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood, New York, 1980, vols. 3, 4; R. Southgate and S. Elson, in 'Progress in the Chemistry of Organic Natural Products,' eds. W. Herz, H. Grisebach, G. W. Kirby, and Ch. Tamm, Springer-Verlag, New York, 1985, p. 1; W. Durckheimer, J. Blumbach, R. Latrell, and K. H. Sheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180.

2 For reviews on carbapenem synthesis, see: T. Kametani, K. Fukumoto, and M. Ihara, *Heterocycles*, 1982, **17**, 463; T. Nagahara and T. Kametani, *ibid.*, 1987, **25**, 729; G. I. Georg, in 'Studies in Natural Product Chemistry,' ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol. 4, p. 431.

3 For leading references, see: J. Fetter, K. Lempert, M. Kajtar-Peredy, and G. Simig, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1135.

4 J. M. Odriozola, F. P. Cossío, and C. Palomo, *J. Chem. Soc., Chem. Commun.*, 1988, 809; F. P. Cossío, J. M. Odriozola, M. Oiarbide, and C. Palomo, *ibid.*, 1989, 74.

5 C. Palomo, F. P. Cossío, A. Arrieta, J. M. Odriozola, M. Oiarbide, and J. M. Ontoria, *J. Org. Chem.*, in the press.

6 G. I. Georg, J. Kant, and H. S. Gill, *J. Am. Chem. Soc.*, 1987, **109**, 1129.

7 (a) T. Yamada, H. Suzuki, and T. Mukaiyama, *Chem. Lett.*, 1987, 293; (b) C. Gennari, G. Shimperna, and I. Venturini, *Tetrahedron Lett.*, 1988, **44**, 4221; (c) E. W. Colvin, D. McGarry, and M. J. Nugent, *Tetrahedron*, 1988, **44**, 4157.

8 W. F. Huffman, K. G. Holden, T. F. Buckley, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, 1977, **99**, 2352; R. Zamboni and G. Just, *Can. J. Chem.*, 1979, **57**, 1945; D. R. Kronenthal, C. Y. Han, and M. K. Taylor, *J. Org. Chem.*, 1982, **47**, 2765; B. Ernest and D. Bellus, Ger. Offen, DE 3 620 467, 1987 (*Chem. Abstr.*, 1987, **106**, 176045).

9 For leading references, see: C. Palomo, F. P. Cossío, J. M. Odriozola, M. Oiarbide, and J. M. Ontoria, *Tetrahedron Lett.*, 1989, **30**, 4577.

10 G. I. Georg and J. Kant, *J. Org. Chem.* 1988, **53**, 692.

11 E. J. Corey and C. V. Kim, *J. Am. Chem. Soc.*, 1972, **24**, 758.

12 D. F. Corbett and A. J. Eglington, *J. Chem. Soc., Chem. Commun.*, 1980, 1083; J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun*, 1980, 1084.

13 I. Fleming and J. D. Kilburn, *J. Chem. Soc., Chem. Commun.*, 1986, 1198.

§ Determined by 300 MHz ^1H NMR spectroscopy from the coupling constants between H-3 and H-1' in both isomers: $J_{1',3}$ for the *syn*-isomer is greater than that for the *anti*-isomer (**17a**): δ 4.14 (dd, $J_{1',3}$ 3.8, $J_{3,4}$ 6.4 Hz, H-3); (**17b**): δ 3.72 (dd, $J_{1',3}$ 3.1, $J_{3,4}$ 6.3 Hz, H-3). See also: F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, 1981, **46**, 2208.

¶ In each case the yield was 76 and 70%, respectively, and the ratio of (**17b**) to (**18b**) was found to be 28 : 38 when the reaction was performed in hexane. In acetonitrile the ratio of *cis*- and *trans*-isomers was 95 : 5 and the ratio of *cis*-diastereoisomers (**17b**) to (**18b**) was 65 : 30.