The α-Bromoester–Imine Condensation promoted by Zinc–Trimethylchlorosilane: A Stereospecific Short Formal Synthesis of (±)-Carbapenem Antibiotics and Related Compounds†

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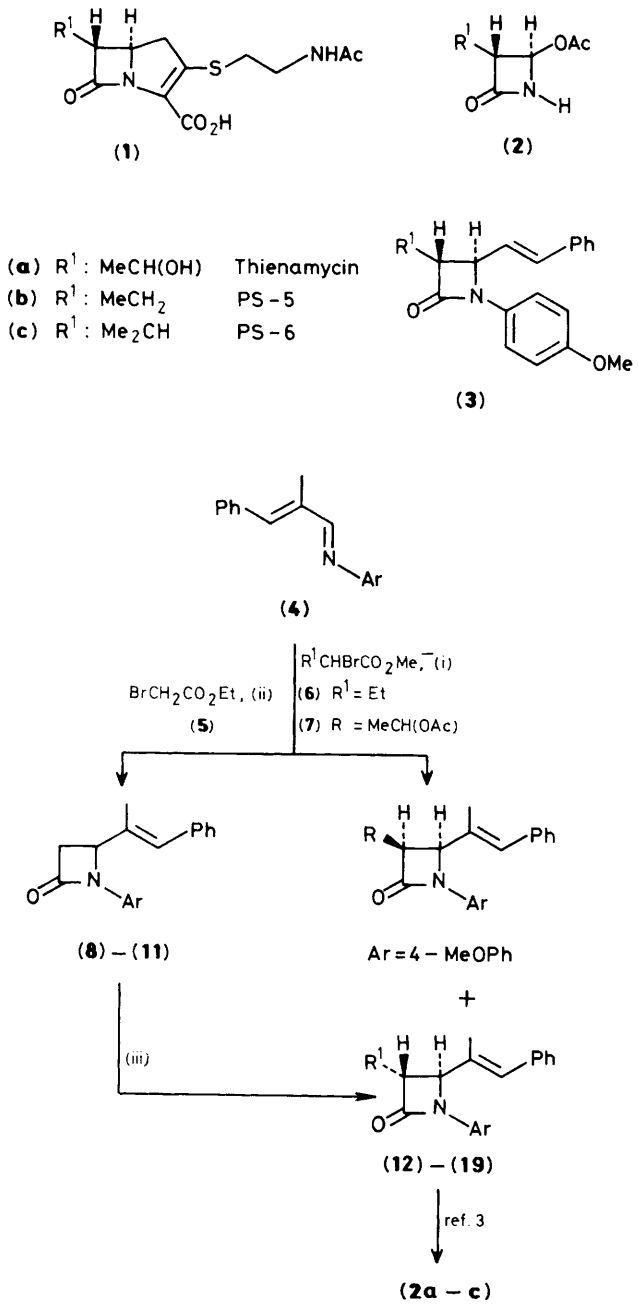
Ethyl bromoacetate reacts with imines in the presence of zinc activated by trimethylchlorosilane to give high yields of 3-unsubstituted β-lactams.

Carbapenem antibiotics (**1**) have attracted a great deal of interest because of their applications from both a biological and a synthetic point of view.[1] Most of the reported syntheses of these compounds involve preparation of the corresponding 4-acetoxy-azetidin-2-one (**2**) starting from appropriately substituted monocyclic β-lactams such as (**3**).[2] We recently undertook[3] a study on the Reformatsky type reaction of Gilman and Speeter[4] between methyl α-bromobutyrate (**6**) and the imine (**4**) to synthesize the (±)-PS-5 carbapenem intermediate (**2b**). However, attempted preparation of the corresponding thienamycin precursor (**16**) (Table 2) starting from (**7**) and the imine (**4**) was unsuccessful‡ (Scheme 1). It has been reported that α-alkylation and α-acylation of a suitable 3-unsubstituted azetidin-2-one is of potential value in β-lactam chemistry since a wide variety of β-lactam compounds can be obtained from a common intermediate.[5]

† Preliminary accounts of this work were presented in 'Euchem Symposium on The Chemical Synthesis of Antibiotics,' Aussois (Savoie), May 2—6, 1988.

‡ This result can be attributed to an easy elimination of the acetoxy group in the starting product (**7**) or in the β-aminoester intermediate formed in the reaction.



Scheme 1. *Reagents and conditions:* (i) Zn, I_2, or $HgCl_2$, toluene, reflux; (ii) Zn, $ClSiMe_3$, benzene, reflux, 2.5 h; (iii) LDA, −78 °C, THF, then electrophile, −78 °C, room temp.

However, of the few direct methods for the synthesis of 3-unsubstituted azetidin-2-ones,[6] the Reformatsky type reaction between ethyl bromoacetate and Schiff's bases afforded low yields of the corresponding β-lactams.[7] In this communication we describe a practical high yield preparation of 3-unsubstituted β-lactams and their further conversion into key compounds for carbapenem synthesis.

We first prepared the β-lactam (**8**) in 53% yield under usual Gilman and Speeter conditions.[3] Since few variations have been studied to optimize the Gilman and Speeter reaction, we attempted to improve the yield by use of different conditions (Table 1). We found that the activation of zinc by trimethylchlorosilane (TMCS)[8] was exceedingly effective in promoting

Table 1. Reaction between (**5**) and (**4**) under different conditions.[a]

Compound	Ar	Solvent[b]	Catalyst	Time/h	Yield (%)[c]
(**8**)	4-$MeOC_6H_4$[d]	Bz	I_2	4	21
		Tol	I_2	4	35
		Bz	$HgCl_2$	4	20
		Tol	$HgCl_2$	8	53
		Bz	TMCS	2.5	95
(**9**)	4-MeC_6H_4[e]	Bz	I_2	2.5	30
		Bz	TMCS	2.5	95
(**10**)	Ph[f]	Bz	I_2	2.5	30
		Bz	TMCS	2.5	80
(**11**)	4-$MeOPhCH_2$[g]	Bz	TMCS	2.5	70

[a] Reactions conducted on 10 mmol scale: 1.2 : 1 : 0.12 : 1 : 0.5 ratio of (**5**), (**4**), I_2, $HgCl_2$, and TMCS. [b] Bz = Benzene, Tol = Toluene. [c] Yields based on weight of isolated product by column chromatography on silica gel. [d] M.p. 138—139 °C. [e] M.p. 81—83 °C. [f] M.p. 113—116 °C. [g] Isolated as an oil.

Table 2. Preparation of β-lactams (**12**)—(**19**).[a]

Compound[b]	Electrophile	R^1	Yield (%)	M.p./°C
(**12**)	Me_3SiCl	Me_3Si	90	108—111
(**13**)	EtI	Et	92	Oil
(**14**)	Pr^iI	Pr^i	70	76—78
(**15**)	MeCHO	MeCHOH	98	Oil
(**16**)		MeCHOAc	93	Oil
(**17**)	Me_2CO	Me_2COH	95	Oil
(**18**)	*p*-$MeC_6H_4SO_2N_3$	N_3	70	Oil
(**19**)		3,5-DNBNH[d]	70	241(d)

[a] Reactions conducted on 5 mmol scale; (**8**) : electrophile 1 : 4. [b] All compounds were racemic and gave satisfactory spectral and analytical data. [c] Yields based on weight of isolated product by column chromatography on silica gel. [d] 3,5-DNB = 3,5-dinitrobenzoyl derivative.

the Gilman and Speeter reaction between ethyl bromoacetate (**5**) and Schiff's bases (**4**) providing an easy access to 3-unsubstituted β-lactams.§ The results summarized in Table 1 illustrate the effectiveness of this catalyst in the synthesis of a variety of 4-(α-methylstyryl) β-lactams in excellent yields. The β-lactam (**8**) thus prepared was treated with lithium diisopropylamide (LDA) at −78 °C in tetrahydrofuran (THF), and the resulting solution quenched with a fourfold excess of an electrophile to furnish the expected *trans*-3,4-disubstituted β-lactams (**12**)—(**19**) in good yield (Table 2). In all cases the reaction was stereospecific and the *trans* relationship of the C-3 and C-4 substituents on the β-lactam ring was unequivocally determined by n.m.r. spectroscopy ($J_{3,4} \approx 2$ Hz). Particularly β-lactam (**15**) was obtained as an equimolar mixture of diastereoisomers epimeric about the hydroxy group which were not separated. From this approach the 3-azido β-lactam (**18**), which serves as a building block for the synthesis of monobactams and nocardicins,[9] was also prepared in good yield. For example, the lithium enolate of (**8**) was treated with toluene-*p*-sulphonyl azide[10] (4 equiv.) under the above conditions and the resulting 3-azido β-lactam (**18**) was treated with triphenylphosphine[11] (4.4 equiv., benzene, reflux, 1 h)

§ The ester–imine condensation as well as the acid chloride–imine approach were unfruitful in synthesizing these 3-unsubstituted β-lactams; see C. Gluchowski, L. Cooper, D. E. Bergbreiter, and M. Newcomb, *J. Org. Chem.*, 1980, **45**, 3413; A. Mujean and J. Chuche, *Tetrahedron Lett.*, 1976, 2905.

followed by hydrolysis with THF–water to give the expected 3-amino compound which was isolated as the 3,5-dinitrobenzoyl derivative (**19**) in 70% overall yield from (**18**).

Following our method,[3] the (±)-carbapenem precursor (**2c**) was prepared in 41% overall yield from (**14**). Similarly the β-lactam (**15**) after protection of the hydroxyl group as the acetoxy derivative (**16**) afforded the (±)-thienamycin precursor (**2a**) in 40% overall yield.

In conclusion we have accomplished a convenient stereospecific route to a wide variety of carbapenem precursors and related compounds from a common 3-unsubstituted azetidin-2-one as starting material and have found a straightforward improved method for carrying out the Gilman and Speeter reaction which may be readily extended to further applications.

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