LITERATURE REVIEW OF THE ESTER ENOLATE IMINE CONDENSATION

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Abstract - A review of the ester enolate imine condensation to give β-lactams and or β-amino esters is presented

CONTENTS

INTRODUCTION

Gilman and Speeter[1] were the first to report the reaction between Reformatsky reagents and imines to give β-lactams (Scheme 1, path **A**). In the last 8 years several research groups have reinvestigated this reaction using modern enolate chemistry (path **B**). In both cases β-amino esters have been isolated suggesting the intermediacy of a metalloamine which cyclises to the β-lactam. Although the related aldol condensation[2] is well understood and in most cases stereochemically predictable, the ester enolate imine condensation appears to be much more complex.

This review will cover the condensation of imines with the enolates of alkyl esters, thioesters and iron acyl complexes.[3] Reformatsky intermediates will be considered enolates[4] and will be included. The closely related Lewis acid catalyzed condensation of silyl ketene acetals and imines[5] is beyond the scope of this review and will not be discussed. Likewise, the reactions of ynolates[6] and cross conjugated enolates[7] with imines will not be discussed.

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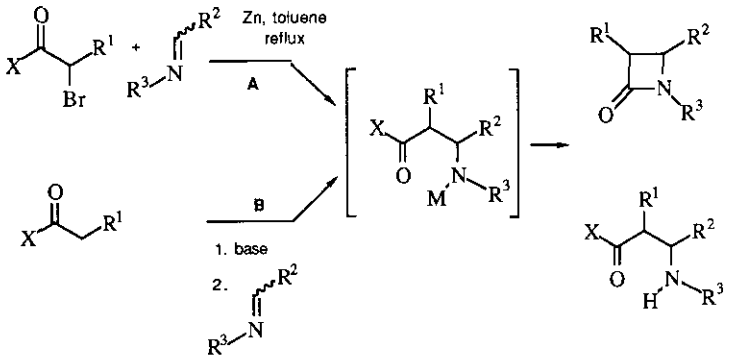
The Ester Enolate Imine Condensation



Of the various ester enolates used in the reaction, it is convenient to consider three separate classes: simple alkyl-substituted, α-hetero-substituted, and the 3-hydroxybutyrates.[8] Likewise the imines can be subdivided as N-aryl, N-alkyl, N-hetero. The following literature survey is presented accordingly.

A. SIMPLE ALKYL ESTER ENOLATES

A.1 N-Aryl Imines

The reaction of simple alkyl ester enolates and imines to give β-lactams are summarized in Table 1A. The original Reformatsky conditions of Gilman and Speeter[1] invoved refluxing a mixture of toluene, ethyl α-bromoacetate and benzalaniline in the presence of zinc foil and a catalytic amount of iodine. The β-lactam product was isolated in 56% yield (entry 1). Kapoor[9] reported a slightly higher yield of the β-lactam by employing pure zinc foil in the reaction (entry 2). A significant increase in yield was observed by Bose[10] when the Reformatsky reaction of ethyl α-bromoacetate and benzalaniline was promoted with ultrasound (entry 3). This sonication procedure is limited to the formation of 3-unsubstituted β-lactams.

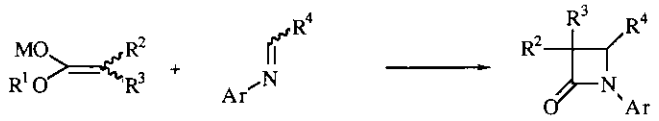
The effect of substituents and reaction conditions on the Reformatsky reaction with imines to give β-lactams has been studied extensively by Kagan[12] and Guademar.[13] When benzalaniline was added to a refluxing mixture of toluene, ethyl α-bromopropionate, zinc and a crystal of iodine, a 73:27 mixture of *cis* and *trans* β-lactams was isolated in 75% yield (Table 1A, entry 4). Increasing the size of the α substituent of the ester from methyl to isopropyl to *t*-butyl (entries 4, 7 and 11) increased the amount of the *trans* isomer formed to where it became the major product. Changing R^1 of the ester from methyl to isopropyl (entries 11 and 12) also favors formation of the *trans* isomer.

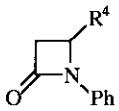
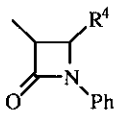
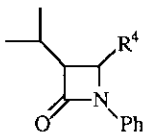
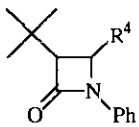
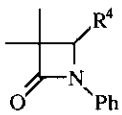
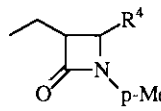
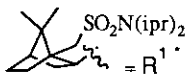
The choice of solvent has a great effect on the stereoisomer ratios in the Reformatsky reaction with imines. When THF was used as the solvent, more of the *cis* β-lactam isomer was isolated than when toluene was employed (compare entries [4 and 5], [7 and 8] and [11 and 13]). A similar effect was observed when benzene was used (compare entries 16 and 17). The mixture of β-lactams shown in entries 16 and 17 has been converted to an intermediate in the synthesis of the carbapenem antibiotic (±)-PS-5.[11]

If the Reformatsky reaction was carried out at -10° C for 24 hours, the sole product isolated was the *erythro* β-amino ester which would cyclize to a *cis*-3,4-disubstituted β-lactam. This result proved to be general for all reactions with N-arylamines

studied by Guademar.[13] Kagan[12] had previously shown that treatment of *erythro* β-amino esters with EtMgBr in Et_2O, gave stereospecifically the *cis* β-lactam in quantitative yield. This two step procedure provides a general route to *cis*-3,4-disubstituted 1-aryl-β-lactams (entry 9).

Table 1A. Condensation of Simple Alkyl Ester Enolates and N-Aryl Imines



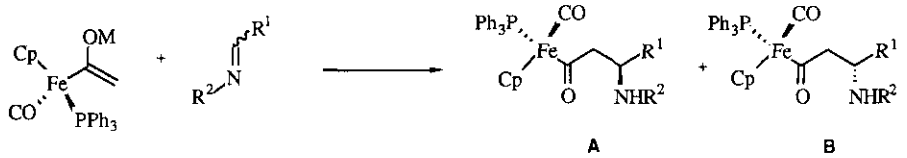
β-lactam	entry	M	R^1	R^4	procedure	yield	*cis:trans*	ref
	1	Zn	Et	Ph	a	56		1
	2	Zn	Et	Ph	a**	58		9
	3	Zn	Et	Ph	b	90		10
	4	Zn	Me	Ph	a	75	73:27	12
	5	Zn	Me	Ph	c	94	80:20	12
	6	Li	Et	Ph	f	47	96:4	15
	7	Zn	Me	Ph	a	98	55:45	12
	8	Zn	Me	Ph	c	92	100:0	12
	9	Zn	Me	Ph	d	87	100:0	12,13
	10	Li	Et	Ph	f	88	99:1	15
	11	Zn	Me	Ph	a	71	25:75	12
	12	Zn	*i*-Pr	Ph	a	93	2:98	12
	13	Zn	Me	Ph	c	96	100:0	12
	14	Li	Et	Ph	f	75		14
	15	Li	Et	H	f	77		16
	16	Zn	Et	CH_3C=CHPh	e	60	33:67	11
	17	Zn	Et	CH_3C=CHPh	a	80	20:80	11
	18	Li	Et	HC=CHPh	f	67	80:20	18
	19	Li	R^1*	HC=CHPh	f	81 (91)***	91:9	17
	20	Li	R^1*	Ph	f	88 (92)***	97:3	17

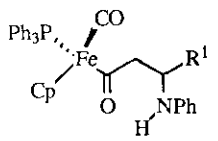
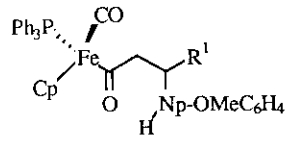
(a) Zn (I_2), toluene, reflux. (b) Zn, (I_2), dioxane, r.t., sonication. (c) Zn (I_2), THF, reflux. (d) Zn (I_2), toluene , -10° C; EtMgBr, Et_2O (e) Zn, (I_2), benzene, reflux. (f) LDA, THF, -70° C to r.t.. ** Pure zinc foil was employed. *** Numbers in parentheses refer to the % ee measured on the *cis* β-lactam.

More recently lithium enolates have successfully been used in the ester enolate imine condensation. Contrary to an early report,[14] monosubstituted (entries 6 and 10) as well as disubstituted esters (entries 14 and 15) can be employed. The 4-unsubstituted β-lactam shown in entry 15 was obtained by treating the corresponding cyanoamine with two equivalents of enolate, which generated the otherwise unstable formaldehyde imine *in situ*.

Attempts to obtain optically active β-lactams from the zinc[12,26] and lithium[14,45] enolates of menthyl esters have met with limited success. However, Hart[17] has demonstrated that high asymmetric induction can be obtained using the lithium enolate of isobornyl 10-diisopropylsulfonamide (entries 19 and 20). The *cis* stereoselectivity observed in the reaction of this chiral lithium enolate with N-aryl imines was higher than that obtained from the ethyl ester (compare entries 18 and 19). The racemic mixture of *cis* and *trans* β-lactams shown in entry 18 was converted to an intermediate in the synthesis of (±)-PS-5[18] and the optically active *cis* β-lactam shown in entry 19 has been converted to an intermediate which can be employed in the synthesis of (+)-PS-5[19].

Table 1B. Condensation of the Enolates of Iron Acyl Complexes and N-Aryl Imines



β-amino acyl iron complex	entry	R^1	M	conditions	A : B	yield	ref
	1	Ph	Li	a	98:2	---	19
	2	Ph	Li	b	92:8	79	20
	3	Ph	*Li*	c	85:15	85	20
	4	Ph	$AlEt_2$	d	85:15	55	20
	5	PhCH=CH	$AlEt_2$	d	57:43	68	21

a. *n*-BuLi, -78°C, solvent not reported. b. LDA, -78° C, THF. c. LDA, -42° C, THF. d. LDA, Et_2AlCl, -42°C, THF.

The lithium enolates of chiral racemic iron acyl complexes readily add to N-aryl imines at -78° C to give β-amino acyl iron complexes with high asymmetric induction (entries 1-3, Table 1B). The diastereoselectivity of the reaction of lithium enolates with benzalaniline appears to depend on the method of enolization (compare entries 1 and 2). Lower reaction temperatures led to a significant loss in diastereoselectivity (compare entries 2 and 3). Good yields of β-amino iron acyl complexes were obtained from diethylaluminum enolates and N-aryl imines as shown in entries 4 and 5. The β-amino iron acyl complexes were converted to the corresponding β-lactams by oxidative decomplexation with cupric chloride,[19] iodine,[20] or bromine.[21]

A.2 N-Alkyl Imines

The reactions of N-alkyl imines with the enolates of simple alkyl esters, thioesters, and iron acyl complexes are summarized in Tables 2A-C. Table 2A distinguishes those reactions that give predominately β-lactam products. When N-alkyl imines and α-bromo esters are subjected to mild Reformatsky conditions (Zn, -10° C), β-lactams and in some cases β-amino esters are isolated (Table 2A). This is in sharp contrast to the similar reaction N-aryl imines, where under the same conditions only β-amino esters were formed. The β-lactams were bad mixtures of *cis* and *trans* isomers. It is interesting that here, as with N-aryl imines, only the *erythro* β-amino esters are found. Entry 4 demonstrates a case of an enolizable imine being employed successfully.

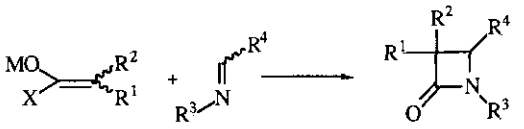
Examples of the reaction of lithium and aluminum ester enolates with N-alkyl imines are shown in entries 5-7. The formaldehyde imine used in entry 5 was generated from the cyanomethyl amine, as mentioned earlier. Akiba[23] has shown that aluminum ester enolates add to enolizable imines to give the *cis* β-lactams in high yields and modest to good stereoselectivity (entries 6 and 7).

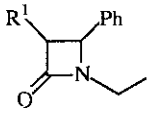
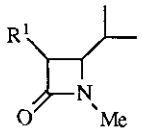
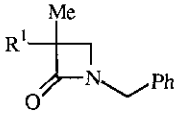
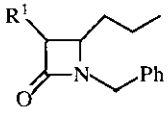
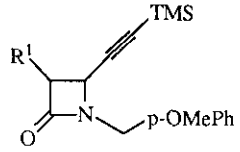
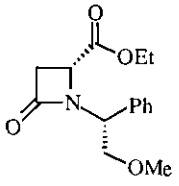
The use of thioester enolates with several different metal counterions has been investigated by Shibasaki[24,27,28] and Mukaiyama.[25] Reactions that give β-lactams in a single step are shown in entries 8-12. In contrast to the dimethylaluminum ester enolates which gave predominately the *cis* β-lactam regardless of the ester substituent (entries 6 and 7), the diethylaluminum thioester enolates favor the formation of the *trans* isomer when the ester substituent is small (entries 8 and 9), and the *cis* isomer when a more sterically demanding ester substituent is used (entry 10). The magnesium thioester enolate reacted in low yield and with almost no stereoselectivity (entry 11).

Table 2B summarizes the synthesis of β-amino esters from the reaction of various metallo thioester enolates with imines. The *erythro* β-amino acid derivatives are the major products with tin and zirconium enolates, but the *threo* isomer predominates with boron enolates regardless of the starting enolate geometry. The reaction of a chiral nonracemic imine with a Reformatsky reagent was first examined by Furukawa[26] (entry 1, Table 2B) and later with tin thioester enolates by Mukaiyama[25] (entry 12, Table 2A and entries 2-6, Table 2B). Although the α-methoxymethylbenzyl group gave slightly higher ee's than the α-methylbenzyl, the *erythro* to *threo* ratio was not as high (entries 2 and 3 *vs.* 4-6). It was also observed that higher ee's were obtained when the tin enolate was prepared from $Sn(OTf)_2$ instead of $SnCl_2$ (entry 2 *vs.* 3). Shibasaki[27] obtained excellent diastereoselectivity with the α-methylbenzyl substituted imine and the boron thioester enolate (entry 7). The β-amino thioester shown in entry 7 was converted to a known intermediate in the synthesis of (+)-PS-5.

The reactions of dialkylaluminum iron acyl complexes with N-alkyl imines are summarized in Table 2C. In these cases the dialkylaluminum enolates were required because the lithium enolate failed to give the desired β-amino acyl complexes. Nonenolizable (entries 1, 3 and 4) as well as enolizable (entries 2, 5 and 6) N-alkyl imines react with the dialkylaluminum enolates of iron acyl complexes in modest to good yields. The β-amino acyl iron complex shown in entry 6 is one of the few examples where a cyclic imine (5, 5 dimethyl-1-pyrroline) was used in the ester enolate imine condensation.

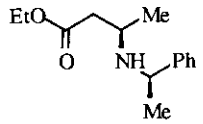
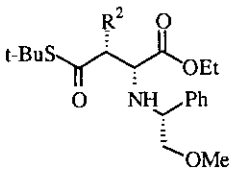
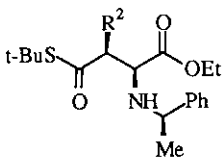
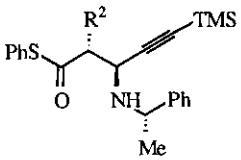
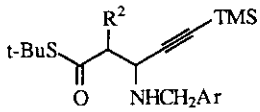
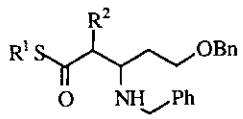
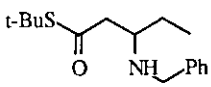
Table 2A. Condensation of Simple Alkyl Ester Enolates and N-Alkyl Imines to Give β-Lactams



β-lactam	entry	X	M	R^1	procedure	yield	*cis:trans*	ref
	1	OEt	Zn	Et	a	41(39)	29:71*	13
	2	OEt	Zn	i-Pr	a	81	62:38	13
	3	OEt	Zn	t-Bu	a	67	34:66	13
	4	OEt	Zn	t-Bu	a	44	not reported	22
	5	OEt	Li	Me	b	66		16
	6	OEt	$AlMe_2$	Me	c	69	76:24	23
	7	OEt	$AlMe_2$	i-Pr	c	58	90:10	23
	8	t-BuS	$AlEt_2$	Me	d	78	20:80	24
	9	t-BuS	$AlEt_2$	Et	d	80	25:75	24
	10	t-BuS	$AlEt_2$	i-Pr	d	73	88:12	24
	11	t-BuS	Mg	Me	e	41	44:56	24
	12	t-BuS	Sn		f	52 (84% ee)**		25

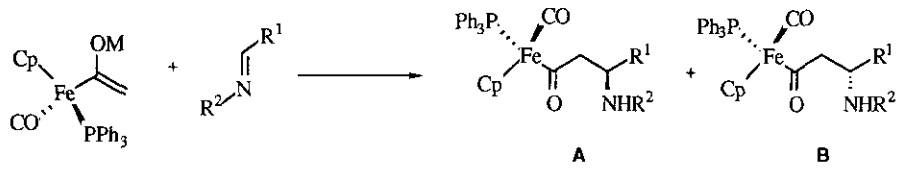
(a) Zn (I_2), CH_3CN, -10° C, 48 h. (b) LDA, THF, -70° C to r.t., 12 h. (c) LDA, THF, Me_2AlCl, -70° to 25° C, 20h. (d) LDA, THF, Et_2AlCl, -78° to 25° C, 4.5 h. (e) LDA, THF, $MgCl_2$, -78° C. (f) LDA, Et_2O, $SnCl_2$. * The number in parentheses represents the % yield of the *erythro* β-amino ester isolated. ** The ee was measured on the debenzylated β-lactam.

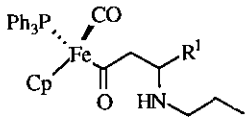
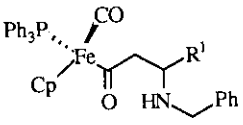
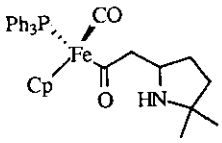
Table 2B. Condensation of Simple Alkyl Ester Enolates and N-Alkyl Imines to Give β-Amino Esters

β-amino ester	entry	M	R^2	procedure#	yield	*erythro*:*threo*	ref
	1	Zn		a	95(26)##		26
	2	Sn	Me	b	85(77)*	75:25	25
	3	Sn	Me	c	81(84)*	67:33	25
	4	Sn	Me	b	78(70)*	91:9	25
	5	Sn	Et	b	78(72)*	95:5	25
	6	Sn	*i*-Pr	b	79(71)*	95:5	25
	7	9-BBN	Et	d	69(95)**	20:80	27
	8	Zr	Me	e	58	80:20	2499
	9	Zr	Et	e	57	86:14	24
	10	Zr	*i*-Pr	e	43	95:5	24
	11	$(C_5H_4)_2B$	Me (R^1=t-Bu)	f(*E*)O	---	33:66	28
	12	9-BBN	Me (R^1=Ph)	f(*Z*)O	73	15:85	28
	13	9-BBN	*i*-Pr (R^1=Ph)	f(*Z*)O	36	10:90	28
	14	Bu_2B		g	43		29

Letters in parentheses refer to enolate geometry.[29b] ## Number in parenthesis refers to ee measured on the debenzylated amino acid. * Numbers in parentheses refer to ee measured on the debenzylated *cis* β-lactam (prepared from the *erythro* amino ester). ** Number in parenthesis refers to the diasteromeric purity of the *trans* β-lactam (prepared from the *threo* amino ester). (a) Zn, benzene, reflux, 2h. (b) LDA, Et_2O, $SnCl_2$. (c) LDA, Et_2O, $Sn(OTf)_2$. (d) 9-BBNOTf, i-Pr_2EtN, CH_2Cl_2, -78° to 0° C followed by imine addition at -40° C. (e) LDA, THF, Cp_2ZrCl_2, -78° C. (f) Reaction conditions not reported. (g) Bu_2BOTf, *i*-Pr_2NEt, Et_2O, 0° to 25° C, H_2O_2.

Table 2C. Condensation of the Enolates of Iron Acyl Complexes and N-Alkyl Imines



β-amino iron acyl complex	entry	R^1	M	conditions	**A : B**	yield	ref
	1	Ph	Et_2Al	a	95:5	80	21
	2	i-Pr	Et_2Al	a	95:5	68	21
	3	HC=CHPh	Et_2Al	a	71:29	44	21
	4	Ph	Et_2Al	a	96:4	75	21
	5	Et	Et_2Al	a	93:7	36	20
	6		i-Bu_2Al	b	57:43	80	21

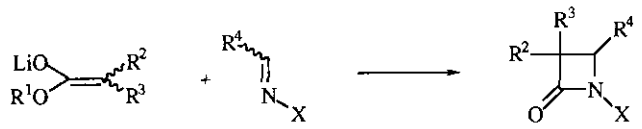
a. LDA, Et_2AlCl, -42° C, THF. b. Conditions not reported.

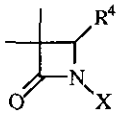
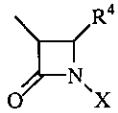
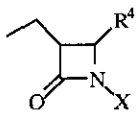
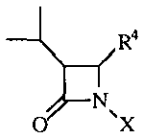
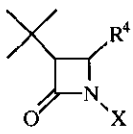
A.3 N-Hetero Imines

A useful variant on the ester enolate imine condensation developed by Hart,[31,15] employs N-trimethylsilyl imines. These intermediates are readily available from treatment of an aldehyde with lithium hexamethyldisilazide. Enolate additions to N-trimethylsilyl imines allow direct formation of the 1-unsubstituted β-lactams upon acid work-up. Representative examples using simple alkyl substituted lithium ester enolates are shown in Table 3. The yields are moderate to good, and, notably, the *cis:trans* ratios are consistently high with the *E* enolates (entries 9, 14 and 18). However, with *Z* enolates poor *cis:trans* ratios are observed (entries 10, 15 and 19).

An earlier report indicated that the condensation of N-silyl imines was limited to nonenolizable imines.[31] However, Cainelli and Panunzio[33] have extended this method to include enolizable imines (entries 11-13). Little change in stereoselectivity resulted upon changing from *t*-butyl propionate to ethyl propionate (entries 11 and 12), but by just changing the imine substituent from methyl to *i*-propyl the *cis trans* selectivity was reversed (entries 12 and 13). The N-trimethylsilyl imines used in the reactions reported in entries 5, 13 and 14 were generated *in situ* by lithium aluminum hydride reduction of the corresponding nitrile and trapping the resulting metalloimine with trimethylsilyl chloride.[32] Formation of the β-lactams did occur when the lithium ester enolates were added directly to the metalloimines, but the yields were much better when trimethylsilyl chloride was present.

Table 3. Condensation of Simple Alkyl Ester Enolates and N-Hetero Imines



β-lactam	entry	X	R^1	R^4	procedure*	yield	*cis:trans*	ref
	1	TMS(H)	Et	Ph	a	72		31
	2	STr	Et	Ph	a	87		34
	3	TMS(H)	Et	C_2H_2Ph	a	41		31
	4	TMS(H)	Et	C_2SiMe_3	a	42		31
	5	TMS(H)	Et	Ph	d	57		32
	6	OBn	Me	H	a	67		35
	7	OBn	Me	Me	a	48		35
	8	OBn	Et	Et	a	40		35
	9	TMS(H)	Et	Ph	a (E)	44	93:7	15
	10	TMS(H)	Et	Ph	b (Z)	44	43:57	15
	11	TMS(H)	Et	Me	c	38	86:14	33
	12	TMS(H)	t-Bu	Me	c	46	78:22	33
	13	TMS(H)	t-Bu	*i*-Pr	c	29	8:92	33
	14	TMS(H)	Et	Ph	a (E)	72	100:0	15
	15	TMS(H)	Et	Ph	b (Z)	66	42:58	15
	16	TMS(H)	Et	*n*-Pr	d	40	50:50	32
	17	TMS(H)	Et	furfuryl	d	56	70:30	32
								
	22	TMS(H)	Et	Ph	a (E)	40	100:0	15

* Letters in parenthesis refer to enolate geometry.[29a] (a) LDA, THF, -70° C, 1h to r.t. 5h to 20h. (b) LDA, HMPA added before enolate formation, THF, -70° C to r.t., 5h. (c) LDA, THF, -78° C to r.t. 8h. (d) LDA, Et_2O, -78° C to r.t., 12 h.

Sulfenimines (entries 2, 20 and 21) and benzyloxyimines (entries 6-8) also react with lithium ester enolates to give β-lactams . The yields are good and these reactions are also applicable to enolizable imines (entries 7,8 and 20).

B. α-HETERO ESTER ENOLATES

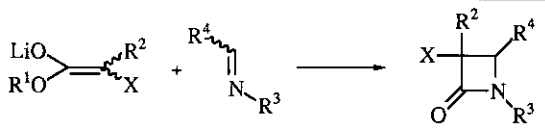
The reactions discussed thus far generate β-lactams with simple alkyl substitution at C-3. Although this has served to partially delineate the scope and limitations of the reaction, most natural and synthetic β-lactams of pharmacological importance possess a heteroatom substituent at C-3.

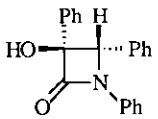
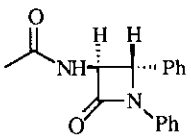
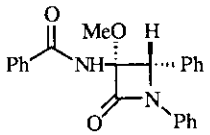
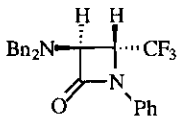
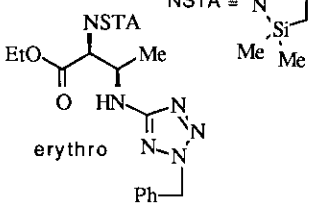
B.1 N-Aryl Imines

In order to introduce a C-3 heteroatom on the β-lactam, the corresponding α-hetero ester must be protected, or a dianion may be used. Examples of the latter with N-aryl imines are shown in Table 4 (entries 1-3). A common feature of these reactions, is that the anionic α-heteroatom substituent on the ester ends up *trans* to the C-4 substituent on the β-lactam.

From entry 4 it can be seen that the requisite glycinate was protected as the dibenzylamine. Reaction of this enolate with N-(2,2,2-trifluoroethylidene)-4-methoxyaniline gave only the *trans* β-lactam. The benzyl groups were removed subsequently *via* catalytic hydrogenolysis to afford the corresponding 3-amino-β-lactam.[37]

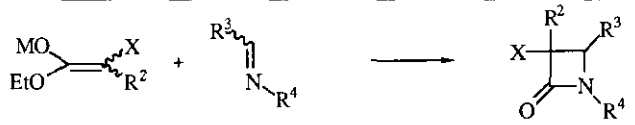
Table 4. Condensation of α-Hetero Ester Enolates and N-Aryl Imines

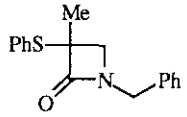
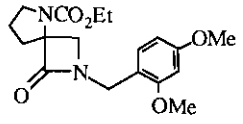
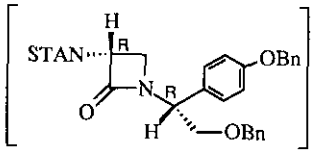
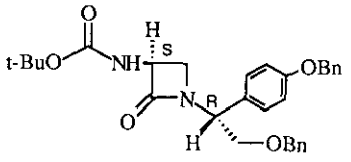
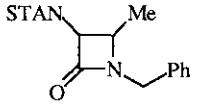
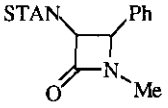


product	entry	procedure	yield	isomer ratio	ref
	1	a	70	*cis:trans* 0:100	14
	2	a	45	*cis:trans* 0:100	14
	3	a	84	*cis:trans* 100:0	36
	4	b	69	*cis:trans* 0:100	37
	5	c	59	*erythro:threo* 74:26	38

(a) LDA, THF, -78° C to r.t., 5 h. (b) LDA, THF, -60° to 0° C, 5 h. (c) LDA, THF, -30° C, 1h.

Table 5A. Condensation of α-Hetero Ester Enolates and N-Akyl Imines



β-lactam	entry	M	procedure**	yield	isomer ratio	ref
	1	Li	a	62		16
	2	Li	a	64		16
 *	3	Li	a(*E*)	72	RR:SR 10:1	16
	4	Li	b	51	RR:SR 1:2	16
	5	Zn	c(Z)	98	*cis:trans* 0:100	39
	6	Zn	c(Z)	97	*cis:trans* 8:92	39

(a) LDA, THF, -70° C to r.t. 5 h. (b) LDA, THF, -70° to -30° C, 4 h. (c) LDA, Et_2O, $ZnCl_2$ * Isolated as the free amine. **Letters in parentheses refer to enolate geometry.[30a]

Alternatively a silyl protected glycinate can be utilized (entry 5) as first demonstrated in the condensation with an enolizable acetaldehyde imine. The products isolated in this case were the β-amino esters which were separated, and individually cyclised to the respective β-lactams.[38]

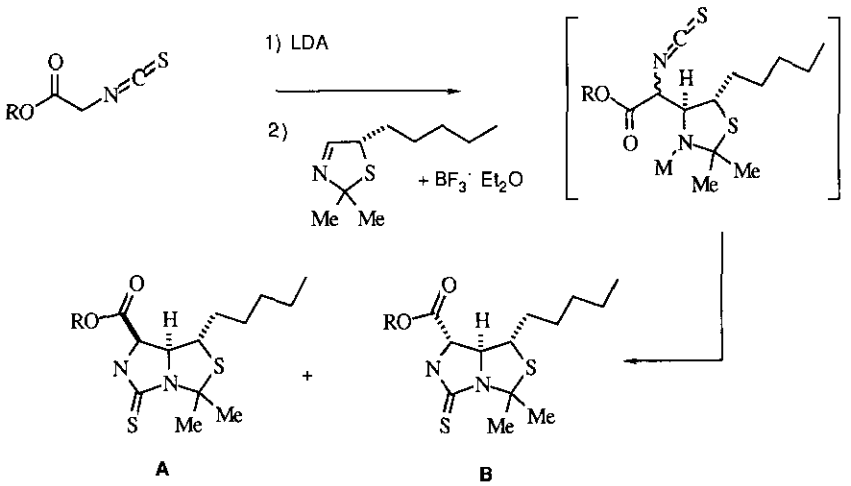
B.2 N-Alkyl Imines

Reaction of the α-hetero-substituted lithium enolates with N-alkyl formaldehyde imines (generated *in situ*) led to the β-lactams shown in Table 5a. When chiral nonracemic cyanomethylamines were used in the reaction with the STA (see Table 4 for the structure of STA) protected lithium ethyl glycinate enolate, excellent diastereoselectivities were observed (entry 3). Enolization to give the (*E*) enolate was established by trapping the enolate as its silyl ketene acetal and performing difference NOE experiments.[16] The relative asymmetric induction could be reversed by using the lithium dianion of the corresponding α-*(acylamino) esters, although the stereoselectivity was poor.*

Van Koten[39] has described a variation where the lithium enolate of a bissilylprotected glycinate is treated with $ZnCl_2$ prior to the addition of the imine (entries 5 and 6). These reaction conditions are very *trans* selective and provide excellent yields, even with enolizable imines. The authors propose that the requisite STA protected zinc enolate possess the (*Z*) geometry, opposite that which was observed with the lithium enolate of the same ester.[16]

In a report by Volkman[40], two of the three chiral centers of biotin were set using the ester enolate imine condensation. Several metal enolates of the isothiocyanatoacetate shown in Table 5B failed to react with the 3-thiazoline. However if the imine was activated with $BF_3{\cdot}Et_2O$ before the enolate was added, the condensation proceeded to give the bicyclic products **A** and **B**. The yields of this condensation ranged from 75-85% and the stereoselectivity increased upon variation of the R group of the ester as shown in entrys 1-4, Table 5B.

Table 5B. Condensation of α-Hetero Ester Enolates with an Activated Imine



entry	R	**A** : **B**
1	Me	58:42
2	CH_2OMe	67:33
3	Et	75:25
4	*i*-Pr	75:25

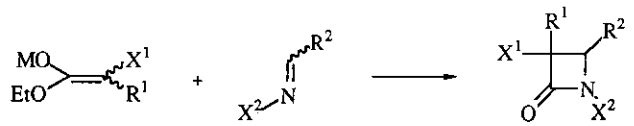
B.3 N-Trimethylsilyl Imines and Sulfenimines

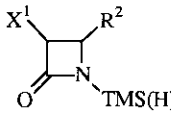
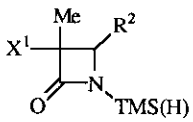
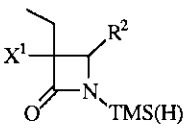
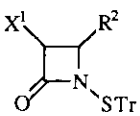
The results of several reactions of α-thiophenoxy enolates with N-trimethylsilyl imines are summarized in Table 6. In a study designed to determine the effect of α-substituents on the ester, it was found that the yield increased and the stereoselectivity was reversed when methyl was substituted for hydrogen (entries 1 and 6). However, when other alkyl groups were used, the yield decreased substantially (entry 8).

An example of a silyl protected glycinate lithium enolate that reacted with high *cis* stereoselectivity with a N-trimethylsilyl imine generated *in situ* (as discussed in section A.3) is shown in entry 2. The corresponding zinc enolates produced the *trans* stereoisomers in lower stereoselectivity (entries 3-5).

Addition of the STA (see Table 4 for the structure of STA) protected lithium glycinate enolate to an enolizable sulfenimine proceeded in good yield to produce the *cis* β-lactam with low stereoselectivity (entry 9).

Table 6. Condensation of α-Hetero Ester Enolates and N-Hetero Imines



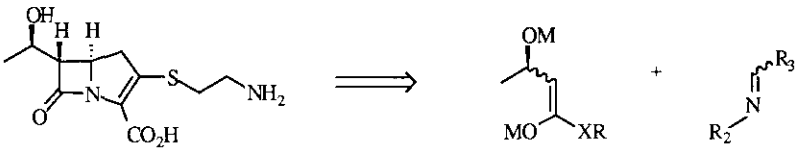
β-Lactam	entry	M	X^1	R^2	procedure	yield	*cis:trans*	ref
	1	Li	SPh	Ph	a	53	91:9	15
	2	Li	NSTA	furfuryl	b	43	95:5	32
	3	Zn	NSTA	Ph	c	90	30:70	39
	4	Zn	$N(TMS)_2$	Ph	c	70	11:89	39
	5	Zn	NSTA	C_2TMS	c	80	7:93	39
	6	Li	SPh	Ph	a	59	31:69	15
	7	Li	SPh	C_2TMS	a	74	73:27	31
	8	Li	SPh	Ph	a	8	25:75	15
	9	Li	NSTA	Me	a	78	83:17	34

(a) THF, -70° C to r.t., 3-40h. (b) LDA, Et_2O, -78° C to r.t., 12h. (c) LDA, Et_2O, $ZnCl_2$, -78° C to r.t.

C. 3-HYDROXYBUTYRATE ENOLATES

Thienamycin **1**, one of the most active members of the carbapenem family of antibiotics, contains three contiguous chiral carbons. Several investigators saw the potential of setting all three centers in one step *via* the ester enolate imine condensation with 3-hydroxybutyrate enolates **2** (eq 1). For convenience in tabulation the derivatives of **2** are drawn as the *R* enantiomer even though a racemic mixture or the *S* enantiomer may have actually been employed in the following reactions.

eq 1



1 2

C.1 N-Aryl Imines

Georg[41-43] has reported the formation of several 1-aryl-3-(1-hydroxyethyl)-β-lactams using the ester enolate imine condensation method (Table 6). Lower reaction temperatures led to increased formation of the one *cis* β-lactam diastereomer **C** (entries 2, 4, 6 and 10). The presence of HMPA in the reaction seems to promote formation of the *trans* diastereomer **B** (entries 5 and 10).

Another trend was observed in the furan series (entries 5-8). Although the yields fluctuated, sequential addition of methoxy groups to the N-phenyl group of the imine, favored formation of the *trans* β-lactam diastereomer **B**.

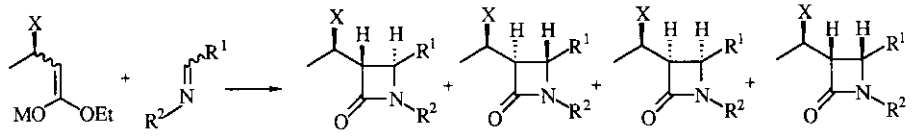
The reaction conditions for the β-lactam forming reactions reported in entries 9-14 have been closely examined. Cainelli[45] found that toluene led to a higher ratio of isomer **C**. Both the **B** and **C** isomers have been used in formal syntheses of thienamycin by Georg[42,43] and Cainelli.[45]

Attempting to improve the stereoselectivity in 3-hydroxybutyrate condensation, Hart[46] investigated the use of the lithium enolate of ethyl β-(dimethylphenylsilyl)butyrate **3** (Table 7), since the silyl substituent can be oxidatively converted to hydroxyl. The presence of HMPA excludes isolation of isomers **C** and **D**. Evidence is presented that epimerisation after β-lactam formation occurs under these conditions. The silyl compounds were converted to the (1-hydroxyethyl)-substituted β-lactams with retention of configuration.

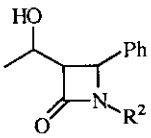
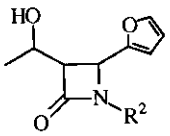
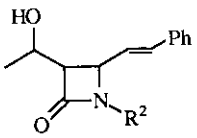
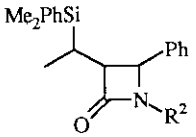
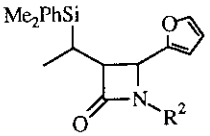
C.2 N-Alkyl Imines

The only reported examples of 3-hydroxybutyrate enolates being added to a N-alkyl imines are shown in Table 8. When the enolizable imine reported in entry 1 was treated with the lithium dianion **2a** none of the desired β-lactam products were isolated. Benzyl alcohol was observed in the reaction mixture, which is probably the result of enolization of the imine followed by β elimination. However, when the corresponding thioester was converted to the boron enolate **2b**, the reaction proceeded in 36% yield to give the β-amino esters which were oxidized to the amino ester derivatives shown. The stereochemistry of these products was determined by ring closure to the β-lactams. Although the overall procedure involves several steps and the yields are low, it is noteworthy that the major diastereomer **A** contains the correct stereochemistry

Table 7. Condensation of 3-Hydroxy Butyrate Ester Enolates and N-Aryl Imines



2a. X = OLi
3. X = Me_2PhSi

β-lactam	entry	R^2	procedure*	yield	A : B : C :D	ref
	1	Ph	a (r.t.)	45	5:95:_ :_	41
	2	Ph	a (-20)	42	_ :60:40:_	41
	3	*p*-$MeOC_6H_4$	a (r.t.)	59	50:50: _: _	41
	4	*p*-$MeOC_6H_4$	a (-20)	50	_ :20:80:_	41
	5	*p*-$MeOC_6H_4$	a (r.t.)	59	50:50: _:_	41
	6	*p*-$MeOC_6H_4$	b (10)	46	20:65:15:_	41
	7	3,4-$(MeO)_2C_6H_3$	a (r.t.)	29	20:80: _:_	41
	8	3,4,5-$(MeO)_3C_6H_2$	a(r.t.)	59	5:95: _:_	41
	9	*p*-$MeOC_6H_4$	a (r.t.)	77	25:50:25:_	41
	10	*p*-$MeOC_6H_4$	a (-20)	67	10:50:40:_	41
	11	*p*-$MeOC_6H_4$	b (-20)	66	_ :50:50:_	41
	12	*p*-$MeOC_6H_4$	b (10)	77	_ :50:50:_	41
	13	*p*-$MeOC_6H_4$	c (-70)	63	15:45:40:_	44
	14	*p*-$MeOC_6H_4$	d (-70)	60	5:34:60:_	45
	15	*p*-$MeOC_6H_4$	e (-70)	66	23:7:53:17	46
	16	*p*-$MeOC_6H_4$	f (-70)	80	76:24:_ :_	46
	17	*p*-$MeOC_6H_4$	g (-70)	80	56:43:_ :_	46
	18	*p*-$MeOC_6H_4$	f (-70)	66	67:33:_ :_	46

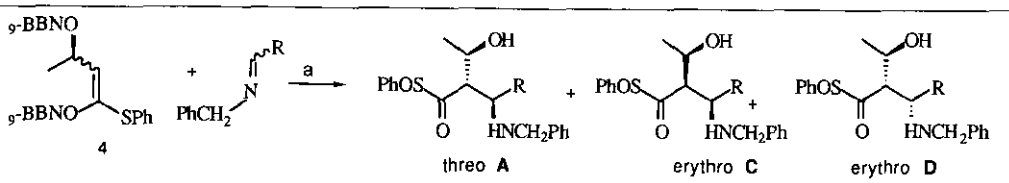
(a) 2 eq LICA (lithium isopropylcyclohexylamide), THF, HMPA. (b) 2 eq. LICA, THF. (c) 2 eq. LDA, THF. (d) 2 eq. LHMDS, tol. (e) LDA, THF. (f) LDA, THF, HMPA. (g) LDA, THF, HMPA added after enolization. * Number in parenthesis is the temperature (in ^{o} C) at which imine addition was done.

required for carbapenem antibiotics. Shibasaki has converted **A** (entry 1) to a known thienamamycin intermediate,[47] and **A** (entry 3) to a known intermediate for the synthesis of 1 β-methylcarbapenem antibiotics.[51]

C.3 N-Silyl Imines

The reaction of the 3-hydroxybutyrate lithium enolate **2a** with N-silyl imines provides the diastereomers shown in Table 9. With THF as the solvent, the *cis* β-lactam isomer **C** was the major product. Starting with optically active **2a**, and after much

Table 8. Condensation of 3-Hydroxybutyrate Ester Enolates and N-Alkyl Imines



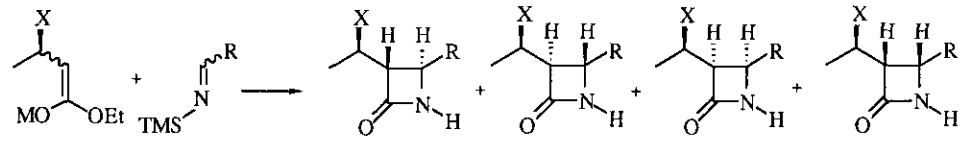
entry	R	yield	*threo* selectivity	A : C : D	ref
1	$(CH_2)_2OBn$	36	88%	88:10:2	47, 28
2	C_2H_2Ph	43	92%	–	28
3	C_2TMS*	55	80-90%	–	51, 28

(a) 9-BBN triflate, *i*-PrNEt, CH_2Cl_2; -20° C to r.t.; H_2O_2. * The TMS group was removed on hydrolysis.

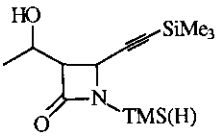
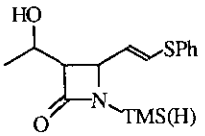
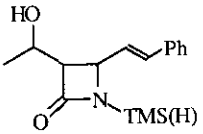
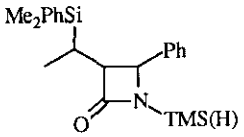
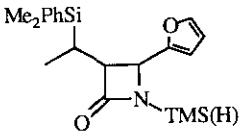
stereochemical manipulation, Nakai[49] converted **C** (entry 2) to a thienamycin intermediate. Likewise Cainelli and Panunzio[50] and Hart[44] have converted the enantiomers of both **B** and **C** (entries 5 and 6) to a known thienamycin intermediate. Addition of HMPA, again enhances formation of the *trans* diastereomer (entry 3).

The highest diastereoselectivities have been observed by Hart[46] using the lithium enolate **3** (entries 7 and 8). Both the furfural and benzaldehyde N-trimethylsilyl imines give exclusively or predominately the *cis* β-lactam **C**.

Table 9. Condensation of 3-Hydroxybutyrate Ester Enolates and N-Trimethylsilyl Imines



2a. X = OLi
3. X = Me_2PhSi

β-Lactam	entry	procedure	yield	A : B : C : D	ref
	1	a	66	1:23:67:10	15
	2	a	50	*[25]:75: –	48,49
	3	b	49	*[63]:37: –	48,49
	4	a	87	3:21:76: –	15
	5	c	50	– :30:70: –	50
	6	a	43	– :37:62: –	51
	7	d	63	1:_:99:_	46
	8	d	72	_:_:100:_	46

(a) 2 eq. LDA, THF, -70° to r.t. (b) 2 eq. LDA, THF, HMPA added before enolization. (c) 2 eq. LHMDS, THF, -78° to r.t. 12h (d) LDA, THF, -70° to r.t. 2h. * Number in brackets represents the combined ratio of a mixture of A and B.

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