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Alkyl(phenylthio)ketenes as Synthetic Equivalents of Monoalkylketenes: A Concise General Route To 3-Alkyl β-Lactams as Carbapenem Building-Blocks.

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Summary: The dehydrochlorination of α-phenylthioalkanoyl chlorides with triethylamine in the presence of imines produced a high yield formation of α-phenylthio β-lactams which upon desulfuration furnished a wide variety of 3-alkyl β-lactams in a high stereoselective fashion.

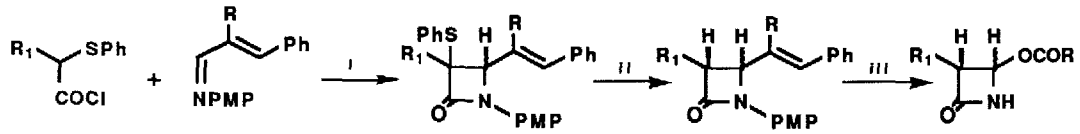
Appropriately substituted monocyclic 3-alkyl β-lactams are important starting materials for the preparation of a wide variety of bicyclic β-lactam antibiotics (ie, carbapenems, olivanic acids, penems and oxapenems)[1]. Recently we have reported on the utility of the α-bromoester-imine condensation to the synthesis of appropriately substituted 3-alkyl β-lactams[2]. Among many other methods for the synthesis of monocyclic β-lactams[3], the ketene-imine cycloaddition reaction[4], or its equivalent, the acid chloride-imine method, has proven to be an exceedingly effective route for the construction of the azetidinone ring[5]. However, the direct preparation of 3-alkyl β-lactams from monoalkylketenes, generated from their corresponding acid chlorides, is often limited in scope[6]. Although some exceptions have recently been appeared[7], no general method to the synthesis of 3-alkyl β-lactams from the ketene-imine approach has been described.

We report here a concise general route to 3-alkyl β-lactams as carbapenem building blocks which involves the use of alkyl(phenylthio)ketenes as synthetic equivalents of monoalkylketenes (Scheme I). Preparation of the 3-methyl β-lactam 8a was examined first. Thus α-(phenylthio)propanoyl chloride 1 with the imine 4a, derived from α-methylcinnamaldehyde and p-anisidine[8], in methylene chloride as solvent afforded, under standard conditions[9], the expected 3-methyl-3-phenylthio β-lactam 5 in 97% yield as a mixture of cis and trans isomers in a ratio 80:20 respectively[10]. When this mixture of isomers was then treated with a slightly excess of tributyltin hydride under azoisobutyronitrile (AIBN) catalysis[11]

Table I. Solvent effect on the stereochemical outcome in the cycloaddition step between imines and α-phenylthioalkanoyl chlorides[a].

Compound[b]	Solvent	Yield, %[c]	cis:trans[d]	Compound[b]	Solvent	Yield, %[c]	cis:trans[d]
5a	CH_2Cl_2	97	80:20	5a	Benzene	95	91:9
5a	CH_3CN	80	72:28	5c	CH_2Cl_2	84	100:0
6a	CH_2Cl_2	86	84:16	6a	Benzene	90	91:9
6a	CH_3CN	85	77:23	6b	CH_2Cl_2	24	64:36
6b	Benzene[e]	72	77:23	6b	CH_3CN[e]	75	57:23
6c	CH_2Cl_2	90	100:0	6c	Benzene	92	100:0
7a	CH_2Cl_2	95	62:38	7a	Benzene	97	86:14
7a	CH_3CN	90	57:43				

[a] Reactions conducted on 10 mmol scale, by addition of the acid chloride to a solution of the imine and triethylamine. [b] All compounds are racemic and were characterized by their physical properties and analytical data. [c] Yields based on weight of isolated product by column chromatography. [d] Determined by 300 MHz nmr spectroscopy: the H-4 proton in the cis isomer appears at lower field than that in the trans isomer. e Addition of the acid chloride at 65°C, then r.t.



(1) R_1: Me (2) R_1: $MeCH_2$ (3) R_1: Me_2CH (4) a R: Me b R: H c R: Ph (5) R_1: Me (6) R_1: $MeCH_2$ (7) R_1: Me_2CH (8) R_1: Me (9) R_1: $MeCH_2$ (10) R_1: Me_2CH (11)

SCHEME I. Reagents and Conditions: i, NEt_3, CH_2Cl_2, r.t. 20-24h.; ii, n-Bu_3SnH, AIBN, toluene, 1-2h.; iii, ref. 2. PMP: p-methoxyphenyl group.

in refluxing toluene for 1.5h, a 92:8 ratio of cis and trans isomers of 8a was efficiently produced in 80% yield. Crystallization from cyclohexane afforded pure cis-8a [mp. 113-115°C; δ 3.60 (dq, H-3), 4.60 (d, J=5.4Hz, H-4)]. The extension of this method to the preparation of the corresponding 3-ethyl and 3-isopropyl analogues is shown in Table I. The following results are particularly noteworthy: first, the stereoselectivity of the cycloaddition step could be notably improved by changing the starting imines 4a and 4b to the more bulky Schiff base 4c[12]; second, the isomer distribution of these 3-alkyl 3-phenylthio β-lactams was found to be strongly dependent upon the solvent media, and the best stereochemical outcome in the cycloaddition step could be obtained when benzene was the solvent of choice. These 3-alkyl-3-phenylthio β-lactams, upon treatment with tributyltin hydride reagent under AIBN catalysis provided the corresponding 3-alkyl β-lactams in excellent yields[13]. As can be seen in Table II, a mixture of cis and trans isomers was generally produced, in which the cis isomer predominate. This high degree of cis stereoselectivity could be explained by assuming that the hydride attack takes place preferentially at the less hindered face of the starting α-phenylthio β-lactam and in the case of 6c, that incorporates a more bulky C_4-substituent, only the corresponding cis isomer of 9c was formed. All of these 3-alkyl β-lactams could be further elaborated by established protocols to furnish important carbapenem precursors, like 11[1].

Table II. 3-alkyl β-lactams prepared[a].

Compound[b]	Yield, %[c]	cis:trans[d]	Compound[b]	Yield, %[c]	cis:trans[d]
8a	80	92:8	9a	97	92:8
9b	87	76:24	9c	97	100:0
10a	91	88:12			

[a] The reduction was performed on a mixture of cis and trans α-alkyl(thiophenyl) β-lactams prepared in methylene chloride as solvent. Reactions conducted on 10 mmol scale in refluxing toluene by using n-Bu_3SnH (1.2 equiv.) and AIBN as catalyst (0.1 equiv.). [b] All compounds are racemic mixtures and were characterized by their physical properties and analytical data. [c] Yields based on weight of isolated product by column chromatography. [d] Determined by 300 MHz nmr spectroscopy: $J_{3,4} \approx 5$ Hz (cis isomer).

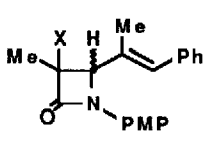
In view of the above results, we tested the scope of our method by examining the reaction between α-phenylthiobutanoyl chloride 2 and Schiff bases 12, that incorporate other suitable substituents for further chemical elaboration. Results of this study are summarized in Table III to illustrate the efficiency, the scope and the applicability of the present method. As can be seen from the results in Table III, imines bearing alkyl substituents at the imine nitrogen atom or carbonyl groups at the imine carbon atom, which can not be used under standard enolate-imine reaction conditions[14], provided the corresponding 3-alkyl-

Table III. (±)PS-5 carbapenem building blocks prepared[a].

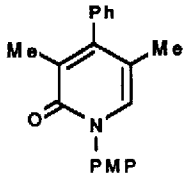
	imine 12[b]		product 13[c]			imine 12[b]		product 13[c]	
	R_1	R_2	Yield, %[d]	cis:trans[f]		R_1	R_2	Yield, %[d]	cis:trans[f]
(a)	PhCO	PMP	95	19:81[g]	(b)	PhC≡C	PMP	90	60:40
(c)	PhCH=CMe	CH_2CO_2Me	74[e]	92:8	(d)	CO_2Me	PMP	89	7:93

[a] Reactions conducted on 10 mmol scale, by addition of the acid chloride to a solution of the imine and triethylamine in benzene as solvent unless otherwise stated. [b] Prepared by standard procedures. [c] All compounds are racemic and were characterized by their physical and analytical data. [d] Yields based on weight of isolated product by column chromatography. [e] In this case the imine was prepared "in situ" and not isolated. [f] Determined by 300 MHz nmr spectroscopy. [g] Reaction performed in methylene chloride as solvent.

3-phenylthio β-lactams 13 in high yields, as valuable intermediates for the synthesis of the (±)PS-5 carbapenem antibiotic[1]. For instance, when the β-lactam 13c was allowed to react with tributyltin hydride under AIBN catalysis, the β-lactam 14c was produced in 80% yield as a mixture of cis and trans isomers in a ratio 82:18 respectively. In a similar way, the β-lactam 13d furnished a 71:29 ratio of cis and trans isomers of 14d. Attempted preparation of the β-lactam 14c directly from butanoyl chloride and the imine 12c was unfruitful[15]; the α-bromoester-imine condensation gave neither the expected β-lactam 14c nor 14d. The use of α-haloalkylketenes[16] as synthetic equivalents of monoalkylketenes was found to be less efficient (Figure I). Reaction between α-halopropanoyl chloride in the presence of triethylamine afforded the β-lactam (15) in 40% yield together with the pyridone (17) in 52% yield. When the reaction was examined with 2-bromopropanoyl chloride, the yield of the expected β-lactam (16) decreased up to 25% and the dehydrobrominated [4+2] cycloadduct (17) was obtained as main product in 70% yield[17].



15 X: Cl
16 X: Br



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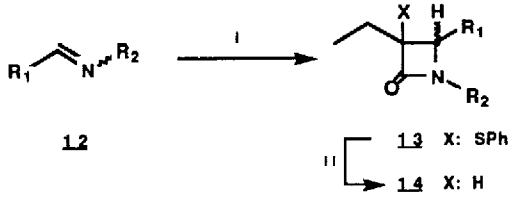

12

13 X: SPh
14 X: H

Figure I. Products obtained in the reaction between α-halopropanoyl chlorides and the imine (4a). 17 m.p. 106-107.5°C (cyclohexane).

SCHEME II. Reagents and Conditions: i, $MeCH_2CH(SPh)$-COCl, solvent, r.t. 20-24 h.; ii, n-Bu_3SnH, AIBN, toluene, reflux.

From the results reported here it is clear that a wide variety of carbapenem building blocks can be obtained by means of alkyl(phenylthio)ketenes as synthetic equivalents of monoalkylketenes[18]. Further studies on the application of this methodology to the synthesis of optically active carbapenem compounds are now underway in our laboratory.

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