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Stereoselective synthesis of trans-disubstituted-β-lactams from *N*-phenylsulfenylimines

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Abstract—*N*-Phenylsulfenylimines derived from aliphatic, aromatic and heteroaromatic aldehydes act as nucleophilic partners in the Staudinger reaction with acetoxyacetyl chloride. Disubstituted-β-lactams are obtained with a surprisingly high trans diastereoselection (up to 99%).

We have recently demonstrated[1] that *N*-sulfenylimines[2] can act as good nucleophilic partners in the Staudinger reaction[3] with alkoxyketenes. *N*-Sulfenyl-β-lactams were obtained in good to excellent yields, but with moderate cis:trans diastereoselectivity. This Letter describes the synthesis of several *trans*-β-lactams by reacting *N*-sulfenylimines with acetoxyketenes and identifies a new stereochemical aspect of the Staudinger reaction.

When an excess (3 equiv) of methoxy- or benzyloxyacetyl chlorides in dichloromethane was added to a solution of imine **1a** containing diisopropylethylamine (3.5 equiv) the reaction produced a mixture of *cis*- and *trans*-β-lactams.[1] However, the same reaction with acetoxyacetyl chloride, under conditions previously optimized, afforded *trans*-β-lactam **2a** in good yield (Table 1). The selective formation of *trans*-β-lactam with acetoxyketene is noteworthy, in sharp contrast with the poor selectivity observed with alkoxyketenes. A possible cis–trans base-catalyzed isomerization of the 3,4-disubstituted-β-lactams, under the reaction conditions, was experimentally ruled out, thus proving that kinetically controlled products were obtained.

The generality of the method is illustrated in Table 1. R may be branched alkyl, aryl substituted with electron donating or withdrawing groups and heteroaromatic substituents. In the series Ph, *i*-Pr, *t*-Bu (entries 1–3), the chemical yield and diastereoselectivity decrease with increasing size of the alkyl group. These results indicate that the size of the imine C-substituent plays a significant role in controlling the stereochemical outcome of the Staudinger reaction. In the series of *N*-phenylsulfenylimines with different substituents on the *C*-phenyl group (entries 4–11), electron-rich substituents like methoxy and methylthio groups (entries 7 and 8) afforded β-lactams with excellent trans selectivity and in high yields. We also investigated the reaction of *N*-sulfenylimines **1d**, **1e**, **1f** and **1k** with different electron-withdrawing substituents on the *C*-phenyl group (entries 4–6 and 11). In these cases, we found lower conversion of imines, lower yields of products and lower trans selectivity.

The effect of the reaction temperature in the product distribution was also analyzed. With *N*-phenylsulfenylimines derived from benzaldehyde or *para*-methylthiobenzaldehyde, respectively, **1a** or **1h**, no change was observed for the experiments conducted at 0 °C. Lower yields were obtained at −40 °C, but the observed trans:cis ratio were practically the same (>99%). With the less reactive *N*-phenylsulfenylimine **1d** derived from *para*-cyanobenzaldehyde, only 20% conversion of imine to β-lactams **2d** was observed at 0 °C with a 69:31 trans:cis product ratio. At −40 °C the reaction was ineffective.

Keywords: *N*-Sulfenylimines; Staudinger reaction; N-Thiolated-*trans*-β-lactams.
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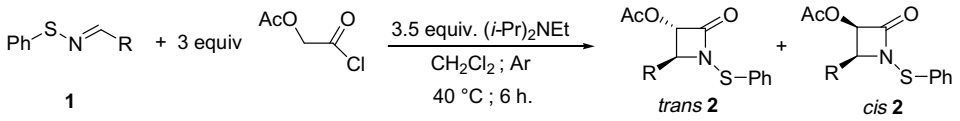
Table 1. Reactions between *N*-phenylsulfenylimines and acetoxyketene



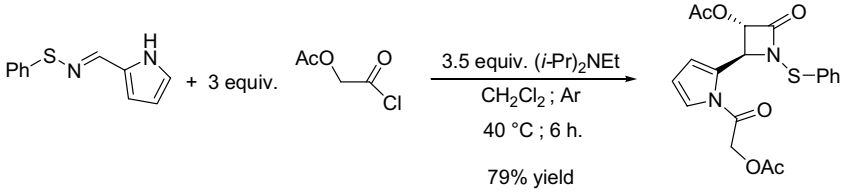
1 *trans* **2** *cis* **2**

Entry	Imine	*E*:*Z*	R	Conversion (%)	Yield (%)	Trans	Cis	β-Lactams
1	**1a**	*E*	Ph	100	89	>99	<1	**2a**
2	**1b**	80/20	*i*-Pr	100	36	>99	<1	**2b**
3	**1c**	*E*	*t*-Bu	100	13	69	31	**2c**
4	**1d**	*E*	*p*-CNC_6H_4	41	21	73	27	**2d**
5	**1e**	*E*	*p*-$NO_2C_6H_4$	16	12	64	36	**2e**
6	**1f**	*E*	*p*-$MeCO_2C_6H_4$	60	46	85	15	**2f**
7	**1g**	*E*	*p*-$MeOC_6H_4$	100	86	>99	<1	**2g**
8	**1h**	*E*	*p*-$MeSC_6H_4$	100	86	>99	<1	**2h**
9	**1i**	*E*	*p*-FC_6H_4	100	82	>99	<1	**2i**
10	**1j**	*E*	*m*-FC_6H_4	100	40	98	2	**2j**
11	**1k**	*E*	*o*-$CF_3C_6H_4$	25	19	90	10	**2k**
12	**1l**	61/39	2-Furfuryl	100	90	>99	<1	**2l**
13	**1m**	90/10	2-Thiophenyl	100	90	>99	<1	**2m**
14	**1n**	*E*	2-Pyrrolyl	100	79	>99	<1	**2n**

This indicates that in the reaction of acetoxyketene with *N*-phenylsulfenylimines, lower temperatures afford lower conversion of imines and lower yield of β-lactams, but do not affect the diastereoselectivity.

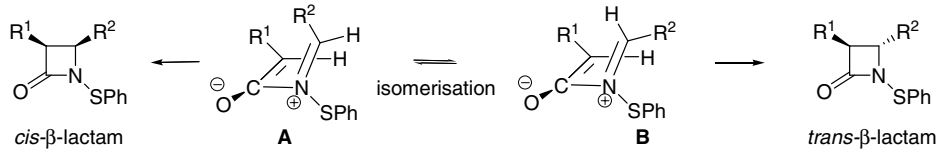
N-Phenylsulfenylimines derived from electron-rich heteroaromatic 2-furanyl and 2-thiophenyl aldehydes **1l** and **1m** (entries 12 and 13) afforded β-lactams **2l** and **2m**, respectively, with excellent trans selectivity and in high yields. The reaction of *N*-phenylsulfenylimine of pyrrole-2-carboxaldehyde **1n** (entry 14) with 3 equiv of acetoxyacetyl chloride resulted in the formation of pure *trans* **2n** in 79% yield (Scheme 1).

According to the model recently published by Xu and co-workers,[4] the analysis of the results collected in Table 1 and their comparison with those observed for the cycloaddition to alkoxyketene suggest an *exo* approach of the ketene for the formation of the zwitterionic intermediate **A**, which may directly affect ring closing to afford cis products (Scheme 2). Alternatively, **A** may undergo a C=N bond isomerization to **B** prior to ring closing thus affording trans products. When *N*-phenylsulfenylimines react with alkoxyketenes, the ring closure competes with the isomerization, thus affording a mixture of cis/trans products.[1] The use of less electron-releasing acetoxy substituent reduces the direct ring closure rate sufficiently to allow a complete C=N isomerization, thus affording pure trans products. This is particularly the case for *N*-phenylsulfenylimine **1g** and **1h** *para*-substituted on the *C*-phenyl group by electron-releasing substituents (OMe, SMe), which increase the rate constant of the isomerization as observed for imidates and thioimidates.[5] This is also the case for *N*-phenylsulfenylimines **1a** and **1b** bearing phenyl or isopropyl C-substituents. Consequently, the stereoselectivity cannot be explained by the configuration of the starting imines. In fact, all *N*-phenylsulfenylimines **1** were determined to be exclusively *E* configuration except imines **1b**, **1l** and **1m** bearing isopropyl, 2-furfuryl and 2-thiophenyl C-substituents, respectively (Table 1, entries 2, 12 and 13). In these three cases, the exclusive forma-



1n *trans* **2n**

Scheme 1. Reactions between *N*-sulfenylimine of pyrrole-2-carboxaldehyde and acetoxyacetyl chloride.



cis-β-lactam **A** **B** *trans*-β-lactam

Scheme 2. Model for the relative stereoselectivity in the Staudinger reaction.

tion of *trans*-β-lactams starting from the mixture of *E*/*Z* imine isomers[6] demonstrates that the isomerization of the imine moiety in the zwitterionic intermediate is faster than the direct ring closure.

Such behaviour of acetoxyketene has some precedents in the literature in its reaction with arylimines derived from bulky amines such as *o*-bromoanilines[7] or polycylic aromatic amines.[8,16]

In conclusion, unprecedented stereoselectivity coupled with simple synthesis of *trans*-β-lactams in good yield was achieved for the first time with *N*-phenylsulfenylimines. This methodology can be extended to a wide variety of substrates.[9] From the synthetic point of view, the unusual trans selectivity can be considered as an added value,[10] as the above results complement the existing method available for the stereocontrolled ketene-imine cycloaddition. Moreover, N-thiolated-β-lactams represent a broad and growing family of bioactive molecules. Following the earlier studies of thiamazins,[17] the recent finding that *N*-methylthio-β-lactams have strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* and, probably, a unique mode of action, opens the door to new investigations.[18]

Acknowledgements

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Supplementary data

Supplementary data (experimental details, synthetic and spectroscopic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.012.

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