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Remarkable ketene substituent dependent effect of photo irradiation on the diastereoselectivity in the Staudinger reaction

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ABSTRACT

Controlling diastereoselectivity is a challenging issue in the Staudinger reaction. The influence of ultraviolet irradiation on the stereoselectivity in the Staudinger reaction has been investigated. The results indicate that ultraviolet irradiation is one of the most important means to regulate the diastereoselectivity of the products in the Staudinger reaction, whatever ketenes were generated from diazomethyl ketones or from substituted acetyl chlorides in the presence of triethylamine. However, the regulation is dependent on the ketene substituents obviously. Ultraviolet irradiation can even reverse the diastereoselectivity for the reactions involving ketenes without strong electron-donating substituents.

The Staudinger reaction, also called the ketene–imine cycloaddition or Staudinger cycloaddition, is one of the most useful methods for the synthesis of β-lactam derivatives,[1] the key structural element of the most widely employed class of β-lactam antibiotics, because of abundant and structurally diverse imine and ketene sources. It is well known that the stereostructure of β-lactam element of the antibiotics plays an important role in their biological activities.[2] Thus, it is still a challenge to prepare β-lactam derivatives with desired and special stereostructures.[1b,e] It has been illustrated that the diastereoselectivity in the Staudinger reactions is governed by the ketene and imine substituents[3] and impacted only by the reaction temperature[4] and the addition sequence of the reactants, rather than other reaction conditions, such as the ketene generation fashion, solvent, additive (including metals and bases),[5] microwave irradiation,[6] etc. Our recent investigation results reveal that the electron-donating ketene substituents, electron-withdrawing imine substituents, and more steric bulky imine *N*-substituents favor the formation of *cis*-β-lactams, adversely, the electron-deficient ketene substituents, electron-rich imine substituents, and less steric imine *N*-substituents favor the formation of *trans*-β-lactams. The competition between the direct ring closure and the iminium isomerization of the zwitterionic intermediates generated from ketenes and imines in the reactions controls the diastereoselectivity.[3] Higher reaction temperature and first mixing imines and acyl chlorides followed by the addition of tertiary amine results in the predominant formation of *trans*-β-lactams.[4,5]

Our previous investigation suggested that the photo irradiation did not impact the diastereoselectivity in the Staudinger reaction involving phenyl diazothioacetate as the ketene precursor with an exceptional example of the reaction involving *N*-4-nitrobenzylidene isopropylamine.[3] But our recent examples indicate that a mixture of *cis*- and *trans*-β-lactams, even *trans*-β-lactams as major products, were obtained in the photo Staudinger reaction of alkyl/aryl diazacetates and imines although thermal Staudinger reactions of alkoxy/aryloxyacetyl chlorides and imines generally produce *cis*-β-lactams as sole or major products.[7] This implies that photo irradiation may regulate the diastereoselectivity in the Staudinger reaction and the effect may be dependent on the ketene substituents. Although several photo Staudinger reactions have been reported,[8,9] the detailed comparison of the diastereoselectivity of the Staudinger reactions under thermal and photo irradiation conditions has seldom been investigated,[3] especially for the Staudinger reactions with different ketenes. This prompts us to investigate the influence of photo irradiation on the diastereoselectivity in the reaction in detail. Both experimental and theoretical investigations indicate that the isomerization of imines and/or the iminium moiety in the zwitterionic intermediates can adjust the diastereoselectivity.[3,10] It was reported that ultraviolet light can isomerize (*E*)-imines and iminiums into (*Z*)-imines and (*Z*)-iminiums and heating can convert (*Z*)-imines and iminiums to their (*E*)-isomers.[11,12] Thus, we assumed that ultraviolet light can regulate the diastereoselectivity in the Staudinger reactions through

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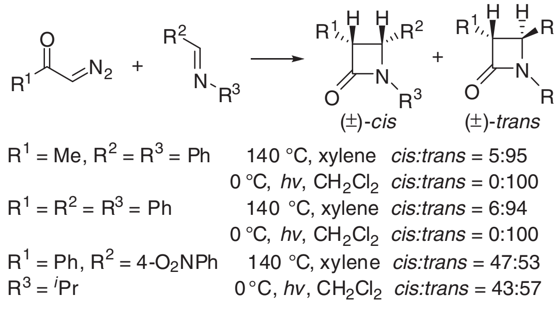
transforming (*E*)-imines and iminiums of the zwitterionic intermediates to their (*Z*)-isomers. Herein, we present the results on the regulation of the diastereoselectivity in the Staudinger reactions with ultraviolet irradiation. This will provide a novel method to regulate the diastereoselectivity in the synthesis of β-lactams via the Staudinger reaction.

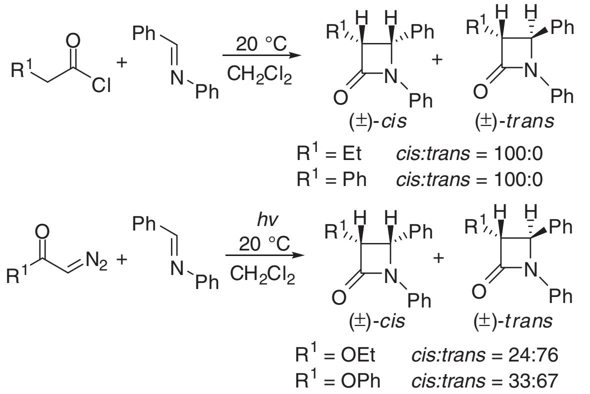
The Wolff rearrangement of diazomethyl ketones and the elimination of substituted acetyl chlorides in the presence of a tertiary amine are the two main pathways to generate ketenes.[13] We first compared the diastereoselectivities between the thermal and photo reactions of diazomethyl ketones and imines (Scheme 1). The thermal reactions of diazoacetone and diazoacetophenone with *N*-benzylideneaniline were conducted, respectively, in 1 mmol scale at 140 °C because the diazomethyl ketones cannot undergo Wolff rearrangement below 130 °C,[3] giving rise to a mixture of *cis*- and *trans*-β-lactams and *trans*-β-lactams as major products in each of the reactions although higher temperature favors the formation of *trans*-β-lactams. The ratio of *cis*/*trans*-products was determined by ^{1}H NMR analysis of the reaction mixture. The same reactions were also carried out at 0 °C under UV photo irradiation. However, the photo reactions produced *trans*-β-lactams as sole products for each of the reactions although lower temperature predominates in the formation of *cis*-β-lactams for thermal reactions. The results indicate that ultraviolet irradiation is advantageous to the formation of *trans*-β-lactams for the Staudinger reactions with diazomethyl ketones as the ketene precursors. To explore the influence of the imine substituents, the reaction of diazoacetophenone and *N*-(4-nitrobenzylidene) isopropylamine was conducted at 140 and at 0 °C under photo irradiation, respectively, producing a mixture of *cis*- and *trans*-β-lactams in 47:53 and 43:57 for *cis*- and *trans*-β-lactams. The results indicate that photo irradiation shows slight influence on the diastereoselectivity in the Staudinger reaction involving ketenes with weak electron-donating substituents. The small stereoselective difference may attribute to the different reaction temperature.

Secondly, we examined the Staudinger reaction involving ketene with strong electron-donating substituents. Ethoxy/phenoxyacetyl chlorides reacted with *N*-benzylidene aniline in dichloromethane at 20 °C to give rise to *cis*-β-lactams as sole products. However, ethyl/phenyl diazoacetates reacted with *N*-benzylidene aniline in dichloromethane at 20 °C under photo irradiation to yield a mixture of *cis*- and *trans*-β-lactams in 24:76 and 33:67, respectively, for *cis*-and *trans*-β-lactams[7] (Scheme 2). The results illustrate that photo irradiation shows certain influence on the diastereoselectivity in the Staudinger reaction involving ketenes with strong electron-donating substituents.

We have compared the thermal and photo Staudinger reactions involving ketenes with electron-withdrawing substituents, such as ethoxycarbonyl recently. *Trans*-β-lactams were obtained in each of the cases.[14]



Scheme 1. Stereoselectivity in reactions of α-diazomethyl ketones and imines.



Scheme 2. Stereoselectivity in reactions of ethoxy/phenoxyacetyl chlorides and ethyl/phenyl diazoacetates with *N*-benzylidene aniline.

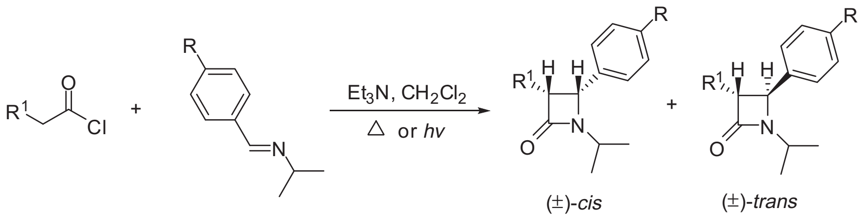
Finally, we conducted the Staudinger reactions with substituted acetyl chlorides as the ketene precursors under both thermal and photo irradiation conditions at the same reaction temperatures because it is unpractical to perform the Staudinger reactions of diazomethyl ketones at the same temperatures under thermal and photo irradiation conditions. To observe the effect of ultraviolet irradiation on the diastereoselectivity obviously, we selected the imines with *C*-electron-rich substituents for the ketenes with electron-donating substituents and the imines with *C*-electron-deficient substituents for the ketenes with electron-withdrawing substituents. The results are summarized in Table 1. The yields and ratios of *cis*/*trans*-products were determined by ^{1}H NMR analysis of the reaction mixture with dimethyl maleate as an internal standard for the determination of the product yields. The ratios of *cis*/*trans*-products were determined on the basis of integrals of the protons on C3 and C4 of the β-lactam ring. The reactions with phenylacetyl chloride only produced products in 1–2% yield at 0 and 20 °C. Thus, the data for these reactions are not shown in Table 1. The results indicate that ultraviolet irradiation improves the ratios of *trans*-β-lactams for all parallel reactions (the same reaction at the same temperature). For the same reaction, the highest ratio of *trans*-β-lactams was obtained at low temperature under ultraviolet irradiation. The diastereoselective difference at the same temperature depends obviously on the ketene substituents. The ketenes with strong electron-donating substituents show less stereoselective differences between thermal and photo reactions at the same temperature than those with weak electron-donating and electron-withdrawing substituents.

In order to further confirm the effect of photo irradiation on the diastereoselectivity of Staudinger reaction, an array of experiments was conducted at 0 °C by employing the selected acyl chlorides with different *N*-substituted imines in the presence of triethylamine. The results are summarized in Table 2. In the way that was expected, the photo irradiation reverses the *cis*/*trans* ratios, compared with the thermal reactions, providing the *trans*-β-lactams as the major or exclusive products. These results indicate that the effect of photo irradiation on the diastereoselectivity in the Staudinger reaction does exist in most cases, which, however, always has been interfered by the effect of substituents on both ketenes and imines, the effect of temperature, and other factors.

The influence of temperature on the diastereoselectivity was investigated previously in the Staudinger reaction.[4] The results revealed that *trans*-products increase with increase of temperature in the temperature range studied. However, an adverse tendency was observed under photo irradiation conditions. That is, *trans*-products decrease with increasing temperature under ultraviolet irradiation. How do we explain the different effects of temperature on

Table 1

Comparison between the thermal and photo Staudinger reactions of substituted acetyl chlorides and imines



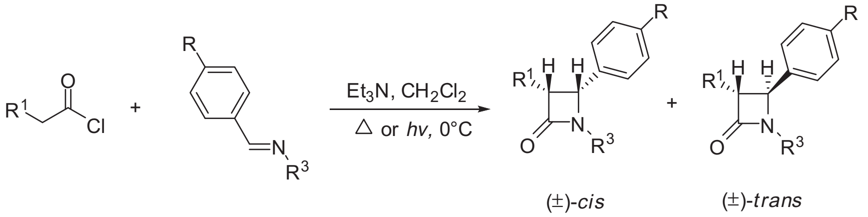
	Cis:*trans*-β-lactams[a]									
Substitution	R^1 = PhO, R = MeO		R^1 = PhthN, R = MeO		R^1 = Cl, R = NO_2		R^1 = Me, R = NO_2		R^1 = Ph, R = NO_2	
Conditions	Δ	hv	Δ	hv	Δ	hv	Δ	hv	Δ	hv
0 °C	69:31	68:32	100:0	0:100	94:6	13:87	100:0	0:100	N.R.	N.R.
20 °C	89:11	78:22	85:15	30:70	92:8	44:56	100:0	11:89	N.R.	N.R.
40 °C	100:0	90:10	87:13	44:56	99:1	52:48	99:1	13:87	88:12	57:43

[a] Determined by ^{1}H NMR spectra of the crude reaction mixture and data given here are the average values derived from at least two independent experimental runs with less than 4% difference.

[b] N.R. indicates no reaction occurs.

Table 2

Diastereoselectivities in the thermal and photo Staudinger reactions of substituted acetyl chlorides with different *N*-substituted imines at 0 °C



Diastereoselectivity	*Cis*/*trans*[a]					
Substitution	R^1 = PhthN, R = MeO		R^1 = Cl, R = NO_2		R^1 = Me, R = NO_2	
Reaction conditions	Δ	hv	Δ	hv	Δ	hv
R^3 = ^{n}Pr	76:24	23:77	92:8	26:74	100:0	16:84
R^3 = *c*Hex	90:10	35:65	96:4	8:92	98:2	0:100
R^3 = Ph	0:100	0:100	N.R.[b]	0:100	70:30	3:97
R^3 = Bn	83:17	28:72	100:0	5:95	100:0	79:21

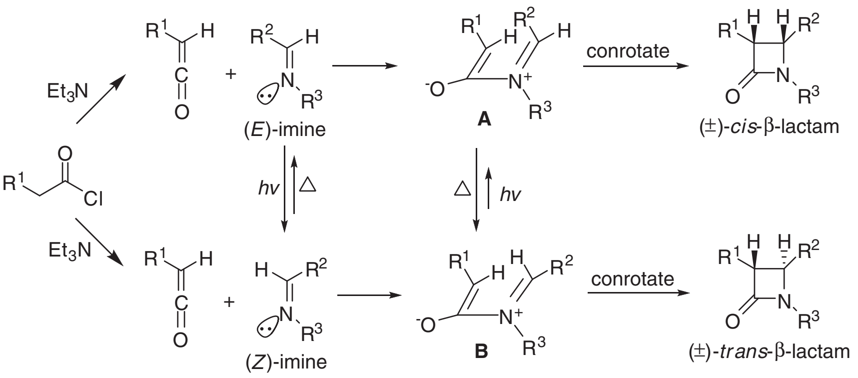
[a] Determined by ^{1}H NMR spectra of the crude reaction mixture and data given here are the average values derived from at least two independent experimental runs with less than 4% difference.

[b] N.R. indicates no reaction occurs.

the diastereoselectivity under thermal and photo conditions? It has been documented that (*E*)-imines and (*E*)-iminiums predominantly convert to (*Z*)-imines and (*Z*)-iminiums under ultraviolet conditions, while (*Z*)-imines and (*Z*)-iminiums favorably isomerize to their stable (*E*)-isomers under heating.[11,12] Thus, for imines, although photo irradiation favorably converts (*E*)-imines to (*Z*)-imines, the concentration of (*Z*)-imines at lower temperature is higher than that at higher temperature under ultraviolet irradiation, and for iminiums, (*E*)-iminiums **B** predominantly convert to (*Z*)-iminiums **A** under ultraviolet conditions at lower temperature, leading to more *trans*-products at lower temperature than at higher temperature (Scheme 3).

When (*E*)-imines convert to (*Z*)-imines under ultraviolet conditions, (*Z*)-imines attack ketenes more favorably than (*E*)-imines to generate intermediates **B** directly, which undergo a conrotatory ring closure to produce *trans*-β-lactams. This is the reason why photo Staudinger reactions produce more *trans*-β-lactams than the corresponding thermal Staudinger reactions at the same temperature.

In summary, the influence of ultraviolet irradiation on the diastereoselectivity in the Staudinger reaction has been investigated via reactions of diazomethyl ketones, diazoacetates, and substituted acetyl chlorides with different imines. The results indicate that ultraviolet irradiation is one of the most important means to regulate the diastereoselectivity of the products in the Staudinger reaction, whatever the ketenes are generated from diazomethyl ketones, from diazoacetates, or from substituted acetyl chlorides in the presence of triethylamine. However, the regulation is dependent on the ketene substituents obviously. Ultraviolet irradiation can even reverse the diastereoselectivity for the reactions involving ketenes without strong electron-donating substituents. The current results provide a novel method to regulate the diastereoselectivity



Scheme 3. Reaction process of substituted acetyl chlorides and imines in the presence of triethylamine under ultraviolet irradiation.

in the Staudinger reactions to prepare β-lactams with desired configurations.

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Supplementary data

Supplementary data (full experimental procedures for the reactions along with relevant spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.003.

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