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# Diastereoselectivity in the Staudinger reaction: a useful probe for investigation of nonthermal microwave effects

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**Abstract**—The effect of microwave irradiation on the selectivity, especially stereoselectivity, is one of the most important issues in microwave-assisted organic reactions. The diastereoselectivity in Staudinger reactions involving the representative ketenes and the corresponding matched imines has been used as a probe to investigate carefully the existence of the specific nonthermal microwave effects. The results indicate that the microwave irradiation-controlled stereoselectivity in the Staudinger reaction is in fact the contribution of temperature. No specific nonthermal microwave effect was found in the Staudinger reaction.

## 1. Introduction

Microwave-assisted organic reactions have been widely developed during the last two decades,[1] especially since several commercially available microwave reactors were designed and manufactured. Recently, microwave irradiation is becoming a powerful technology to accelerate synthetically useful thermal organic reactions. In comparison with conventional heating, microwave irradiation heating shows some advantages:[1a,d] (1) heating via the energetic coupling at the molecular level, (2) heating at a rapid rate, (3) heating volumetrically, (4) heating selectively depending on the properties of materials. Microwave-assisted organic synthesis is characterized by the spectacular acceleration with higher yields under milder reaction conditions during shorter reaction time due to the fast heating rate, which could not be reproduced by conventional heating. Many processes can be improved and even reactions that do not occur with conventional heating can be performed with the use of microwave irradiation (previous view-point). Some microwave-assisted organic reactions were reported to show some different behaviors compared with the corresponding thermal reactions under conventional heating conditions.[1a,d] Recently, microwave irradiation has also been used in some of the diastereoselective and enantioselective reactions with excellent results achieved.[2,3] Thus, the effect of microwave irradiation on the stereoselectivity, including diastereoselectivity and enantioselectivity, is one of the most important issues in microwave-assisted organic reactions.[4]

The Staudinger reaction (the [2+2] ketene–imine cycloaddition reaction) has been widely used to synthesize β-lactam (2-azetidinone) derivatives,[5] which are important intermediates in synthetic and pharmaceutical chemistry fields.[6,7] The reaction of a ketene and an imine can produce *cis*-, *trans*-, or mixtures of *cis*- and *trans*-β-lactam derivatives. Thus, the cis/trans selectivity (diastereoselectivity) is one of the critical issues in the Staudinger reaction. After a series of investigations into the Staudinger reaction between cyclic imines and various ketenes,[8] we have recently proposed a model that can successfully explain and predict the stereoselectivity in the Staudinger reaction.[9] We also investigated factors, which might affect the diastereoselectivity in the Staudinger reaction[10] and found that temperature obviously effects diastereoselectivity in most cases, which depends on the ketene substituents.[11] Manhas et al. reported that microwave irradiation-controlled the diastereoselectivity.[12] This is contradictory to our previous result that no effects of microwave irradiation on the stereoselectivity were observed in several special examples with *N*-benzylidene *tert*-butylamine as an imine.[9] We considered the microwave-controlled stereoselectivity possibly resulted from different temperatures generated under different microwave power outputs.[12] On the other hand, it is still incompletely clear whether the special microwave effect (also called nonthermal microwave effect) exists in the microwave-assisted organic reactions,[1a,c,d] although some carefully investigated experiments indicate that no nonthermal microwave effect exists in the microwave-assisted reactions.[13] The Staudinger reaction can be used as a probe to detect whether the specific microwave effect exists via determination of its diastereoselectivity. Thus, we conducted the investigation into the effect of microwave irradiation on the diastereoselectivity in the Staudinger reaction and present herein our experimental

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*Keywords*: Diastereoselectivity; Imine; Ketene; β-Lactam; Microwave; Nonthermal effect; Staudinger reaction; Stereoselectivity; Temperature.

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results. Additionally, it was found that microwave-assisted asymmetric organocatalyses, including proline-catalyzed asymmetric aldol and Mannich reactions, have been used as a probe to identify the existence of nonthermal microwave effect via determination of their enantioselectivities when we revised our manuscript.[14]

## 2. Results and discussion

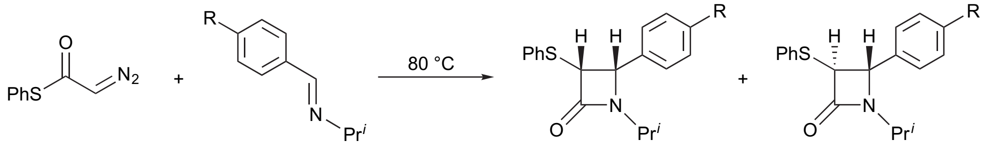
The Staudinger reaction is a stepwise reaction involving nucleophilic attack of an imine to a ketene, giving rise to a zwitterionic intermediate, which undergoes directly a ring closure to produce a *cis*-β-lactam product, or undergoes an isomerization of the imine moiety in the zwitterionic intermediate to form a sterically more favorable intermediate, which subsequently undergoes the ring closure to produce a *trans*-β-lactam product. The competition between the direct ring closure and the isomerization of the zwitterionic intermediate controls the diastereoselectivity.[9] The competition is mainly controlled by the electronic effect of the ketene and imine substituents,[9] the steric hindrance of the imine *N*-substituent,[9] and the reaction temperature.[11] Solvents, additives, and the ketene generations affect the diastereoselectivity slightly.[10]

We previously investigated systematically diastereoselectivities of a series of clean Staudinger reactions involving imines with different electronic effect substituents and phenylthioketene generated from *S*-phenyl 2-diazoethanethioate (**1a**) under thermal (at 80 °C) and photoirradiation conditions.[9] Because microwave irradiation is dielectric heating, resulting from dipolar polarization as a consequence of dipole–dipole interactions between polar molecules and the electromagnetic field, only polar molecules selectively absorb microwaves, nonpolar molecules are inert to microwave dielectric loss in the reaction system.[1a] For polar solvents, the interaction may occur between microwaves and both polar solvents and reactants (for the Staudinger reaction, ketenes, imines, and the intermediates are more polar molecules). Both solvents and reactants (including the intermediates) would be heated via absorbing microwaves simultaneously as done by conventional heating. In these cases, it would be expected that any specific microwave effects would be masked. More interesting cases are reactions conducted in nonpolar solvents. Because, in these cases, the solvents only weakly absorb microwaves, while the reactants and intermediates specifically absorb microwaves. The energy transfer occurs from the reactants and intermediates to the solvents. Thus, the reactants and intermediates locate in these cases in higher energy region, that is, the so-called microscopic hot spots. The diastereoselectivities of reactions under microwave irradiation may be different from those under conventional heating conditions. It would be expected that the specific microwave effect might be obvious and could be observed if it exists. Clearly, the solvent effect seems to be of great importance with regard to the possibility of the specific microwave effect.

To compare with our previously reported results,[10] at first, we conducted the same series of Staudinger reactions involving imines with different electronic effect substituents under microwave irradiation both in a polar solvent (acetonitrile, a favorable microwave absorbance solvent with loss factor tan $\delta$ 0.062)[1c] and in a nonpolar solvent (toluene, a disfavorable microwave absorbance solvent with loss factor tan $\delta$ 0.040)[1c] at 80 °C. To avoid the effect of different heating rates in the conventional heating and the microwave irradiation heating and to compare as strict as possible, the ketene precursor **1a** was added into the fine temperature-controlled reaction system after the temperature of the reaction system was stable at the desired value. (All temperature-controlled reactions in this article were conducted in this mode.) For each of the reactions, the ratios of *cis*- and *trans*-β-lactam products were determined via $^1$H NMR spectra of the crude reaction mixture. The diastereoselective data are presented in Table 1 and Hammett plots of these four series of reactions are shown in Figure 1. The results indicate that no obvious effect of microwave irradiation on the diastereoselectivity was observed in the Staudinger reactions involving imines with different electronic effect substituents.

Secondly, to study the effect of microwave irradiation on the diastereoselectivity of Staudinger reactions involving ketenes with different electronic effect substituents at different temperatures, we investigated a series of Staudinger reactions involving the different representative ketenes and

**Table 1**. Diastereoselectivity in the thermal and microwave-assisted Staudinger reactions involving different imines



**1a** **2** (±)−*cis* −**3** (±)−*trans* −**4**

**2**, **3**, **4**: **a**: R=MeO, **b**: R=Me, **c**: R=H, **d**: R=Cl, **e**: R=$CF_3$, **f**: R=$NO_2$

| Entry | Solvent | Reaction conditions | cis/trans[a] | | | | | | $\rho$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | **3a/4a** | **3b/4b** | **3c/4c** | **3d/4d** | **3e/4e** | **3f/4f** | | |
| 1 | Toluene | Δ | 4:96 | 7:93 | 12:88 | 17:83 | 42:58 | 77:23 | 1.68 | 0.98 |
| 2 | Toluene | MWI | 3:97 | 5:95 | 10:90 | 19:81 | 44:56 | 77:23 | 1.85 | 0.99 |
| 3 | MeCN | Δ | 3:97 | 7:93 | 11:89 | 15:85 | 40:60 | 71:29 | 1.66 | 0.97 |
| 4 | MeCN | MWI | 4:98 | 6:94 | 6:94 | 16:84 | 37:63 | 70:30 | 1.66 | 0.98 |

[a] Data are the average values derived from two independent experimental runs with less than 4% difference.

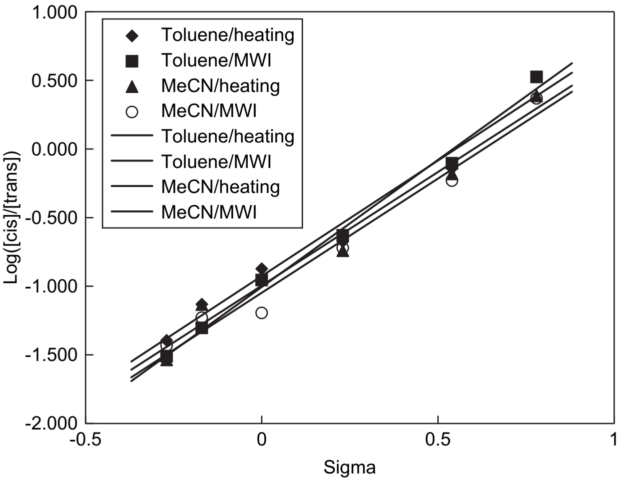
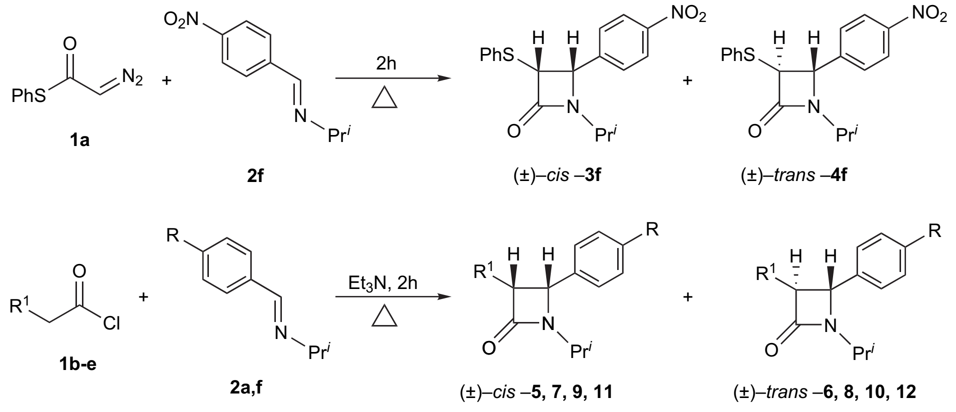


**Figure 1**. Hammett plots of the thermal and microwave-assisted Staudinger reactions involving different imines.

the corresponding matched imines. To observe obviously the different cis/trans ratios of β-lactam products produced from different ketenes over a broad temperature range, we needed to select suitable imines for the different ketenes. For the ketenes with methyl, chloro, and phenylthio substituents, which favor *trans*-β-lactam products, the imine **2f** with *C*-*p*-nitrophenyl substituent was selected for favoring the formation of *cis*-β-lactams. For ketenes with phenoxy and phthalimido substituents, the imine **2a** with *C*-*p*-methoxyphenyl substituent was selected for favoring the formation of *trans*-β-lactams. The selected Staudinger reactions were conducted in nonpolar aromatic solvents at 60, 80, 110, and 150 °C. The temperature was controlled carefully and the ratios of *cis*- and *trans*-β-lactam products were determined via $^1$H NMR spectra of the crude reaction mixture. The results are summarized in Table 2. The results indicate that no obvious effect of microwave irradiation on the diastereoselectivity was observed in most cases (less than 5% difference between the thermal and microwave irradiation conditions). Although some effects (more than 5% difference) were observed in some cases, for example methylketene at 60 and 80 °C, chloroketene at 110 °C, and phthalimidoketene at 80 and 110 °C, we are prone to consider that these differences were caused by the temperature differences under microwave irradiation because the reactants and their intermediates should locate in microscopic hot spots in the reaction systems and their actual temperature is somewhat higher than the solvent. That is, the microwave-assisted reactions occur actually at a little higher temperature than the indicated one. The temperatures where some differences were observed are sensitive temperatures for these ketenes, respectively, on the basis of our previous results on the effect of temperature on the diastereoselectivity in the Staudinger reaction.[11] For example, the diastereoselectivity of the methylketene-participated Staudinger reaction is sensitive in the low temperature region. These changes in diastereoselectivities are in great accordance with the ketenesubstituent-dependent effect of temperature on the diastereoselectivities observed previously.[11] The results indicate that no obvious effect of microwave irradiation

**Table 2**. Diastereoselectivity in the thermal and microwave-assisted Staudinger reactions involving different ketenes at different temperatures



**1b, 5, 6**: R$^1$ = Me, **1c, 7, 8**: R$^1$ = PhO, **1d, 9, 10**: R$^1$ = Cl, **1e, 11, 12**: R$^1$ = PhthN
**2a, 7, 8, 11, 12**: R = MeO; **2f, 5, 6, 9, 10**: R = NO$_2$

| Entry | Reaction temperature (°C) | Reaction conditions | Solvent | cis/trans[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | **3f/4f** | **5/6** | **7/8** | **9/10** | **11/12** |
| 1 | 150 | Δ | Mesitylene | 77:23 | 42:58 | 59:41 | 45:55 | 4:96 |
| 2 | 150 | MWI | Mesitylene | 82:18 | 41:59 | 54:46 | 42:58 | 6:94 |
| 3 | 110 | Δ | Toluene | 84:16 | 42:58 | 75:25 | 71:29 | 51:49 |
| 4 | 110 | MWI | Toluene | 81:19 | 42:58 | 70:30 | 63:37 | 19:81 |
| 5 | 80 | Δ | Toluene | 77:23 | 60:40 | 96:4 | 89:11 | 72:28 |
| 6 | 80 | MWI | Toluene | 75:25 | 52:48 | 95:5 | 86:14 | 58:42 |
| 7 | 60 | Δ | Toluene | 70:30 | 77:23 | >99:1 | 95:5 | 80:20 |
| 8 | 60 | MWI | Toluene | No rxn | 70:30 | >99:1 | 95:5 | 81:19 |
| 9 | 80 | Δ | DCE | | 78:21 | 98:2 | 94:6 | |
| 10 | 80 | MWI | DCE | | 70:30 | 97:3 | 91:9 | |

[a] Data are the average values derived from two independent experimental runs with less than 4% difference.

on the diastereoselectivity was observed in the Staudinger reactions involving ketenes with different electronic effect substituents.

To further validate our assumption, we also conducted reactions involving methylketene, phenoxyketene, and chloroketene at 80 °C in a more favorable microwave absorbance solvent 1,2-dichloroethane (DCE) (loss factor tan $\delta$ 0.127).[1c] The same differences in the diastereoselectivity were observed as those in toluene (see Table 2, entries 5, 6, 9, and 10). The results may be rationalized as follows: reactants and intermediates in the Staudinger reactions are much more polar than solvents, no matter toluene or DCE. It should be noted that, unlike our previous results,[10] the cis-selectivity in DCE is higher than that in toluene for the selected Staudinger reactions, which is in agreement with the computational results of Cossio et al.,[15] but different from the results of the phenylthioketene-participating Staudinger reactions.[10] This indicates that the effect of solvent on the diastereoselectivity is also ketene substituent-dependent.

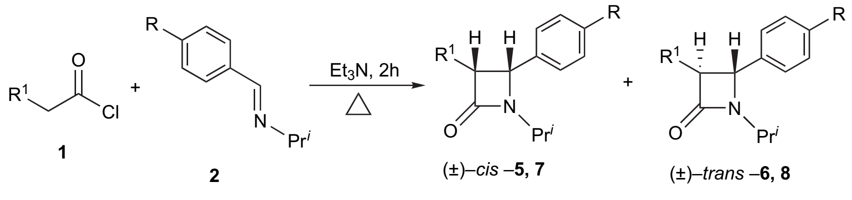
Manhas et al. observed previously that microwave power outputs affected the diastereoselectivity in the Staudinger reaction.[12] To further investigate the effect, additionally, we selected two representative ketene–imine systems to conduct Staudinger reactions at different microwave power outputs. To verify whether the temperature controls the diastereoselectivity, each of the reactions was conducted in two different aromatic solvents with similar polarity and different boiling points. The results are summarized in Table 3. In toluene–mesitylene solvent system (toluene for 10–60 W and mesitylene for 80–150 W), higher power outputs provide high temperatures (Table 3, columns 4 and 8) because solvents with high enough boiling points were used. The reactions show similar effects of temperature on the diastereoselectivity (Table 3, columns 3 and 7) to those observed under thermal conditions.[11] However, it has been found that the reactions conducted in benzene at above 40 W show similar (almost same) diastereoselectivity (Table 3, columns 5 and 9), respectively, for each of both reaction systems because the reaction temperature was maintained by the boiling point of benzene (Table 3, columns 6 and 10). In benzene, reactions were conducted actually at almost the same temperature range 91–101 °C at above 40 W. The superheating effect was observed. Thus, similar (almost same) diastereoselectivity was observed in benzene. Now it could be concluded that the diastereoselectivity is indeed controlled by temperature and not by the microwave power output.

On the basis of our previous results,[11] trans selectivity increases generally with increasing temperature for most Staudinger reactions, especially for Staudinger reactions involving methyl, chloro, phenoxy, and phthalimidoketenes. Generally, the microwave-assisted Staudinger reactions show higher trans selectivity than the thermal reactions at the same indicated temperature because their reactants and intermediates exist actually in the higher temperature region (microscopic hot spots) in the reaction system. Thus, we conclude that the difference of the diastereoselectivities between the thermal and microwave-assisted Staudinger reactions at the same indicated temperature should be attributed to the temperature gradient in the microwave-assisted reaction system.

## 3. Conclusion

In summary, the effect of microwave irradiation on the diastereoselectivity in the Staudinger reaction was investigated systematically with different imines with phenylthioketene at the same temperature, and with different ketenes and the corresponding matched imines both at different temperatures and under different microwave power outputs. The results indicate that the microwave-controlled diastereoselectivity was caused by different temperatures generated under different microwave irradiation power outputs. Microwave irradiation cannot change the diastereoselectivity in

**Table 3**. Influence of the microwave irradiation power on the diastereoselectivity in the Staudinger reaction



**1b, 5, 6**: $R^1$ = Me, **1c, 7, 8**: $R^1$ = PhO; **2a, 7, 8**: R = MeO; **2f, 5, 6**: R = $NO_2$

| Entry | Microwave power (W) | **5/6** in ArH | | **5/6** in PhH | | **7/8** in ArH | | **7/8** in PhH | |
|---|---|---|---|---|---|---|---|---|---|
| | | cis/trans[a] | Temp (°C) | cis/trans[a] | Temp (°C) | cis/trans[a] | Temp (°C) | cis/trans[a] | Temp (°C) |
| 1 | 150 | 41:59 | 164–174[b] | 40:60 | 96–99 (*R*) | 47:53 | 161–168[b] | 92:8 | 99–101 (*R*) |
| 2 | 100 | 42:58 | 140–158[b] | 42:58 | 98–101 (*R*) | 56:44 | 160–163[b] | 88:12 | 93–96 (*R*) |
| 3 | 80 | 44:56 | 123–123 (*R*)[c] | 43:57 | 93–94 (*R*) | 70:30 | 140–144[b] | 92:8 | 89–93 (*R*) |
| 4 | 60 | 45:55 | 114–118[c] | 43:57 | 92–93 (*R*) | 81:19 | 108–115[c] | 89:11 | 91–92 (*R*) |
| 5 | 40 | 41:59 | 95–103[c] | 44:56 | 84–87 | 91:9 | 106–109[c] | 92:8 | 90–93 |
| 6 | 20 | 43:57 | 68–81[c] | 54:46 | 69–77 | 98:2 | 91–94[c] | 97:3 | 72–75 |
| 7 | 10 | 56:44 | 60–68[c] | 63:37 | 55–64 | >99:1 | 71–76[c] | >99:1 | 74–66 |

[a] Data are the average values derived from two independent experimental runs with less than 4% difference.

[b] In mesitylene.

[c] In toluene, R=refluxing.

the Staudinger reaction. The difference of the diastereoselectivities between the thermal and microwave-assisted Staudinger reactions at the same temperature is attributed to the temperature gradient generated in the microwave-assisted reaction system because their reactants and intermediates are more polar than solvents and they favorably absorb microwaves to get more energy than solvents. That is, they exist actually in the higher temperature region (hot spots) in the reaction system. On the basis of our experimental results, no specific microwave nonthermal effect exists in the Staudinger reaction. More careful investigation into the previously reported nonthermal microwave effect examples indicates that no nonthermal microwave effect exists in the microwave-assisted reactions.[13] Most of the previously reported nonthermal microwave effect examples were generated because the reactions were conducted at actually different temperature[12] or under different reaction conditions. For example, thermal reaction was conducted in solution, while the corresponding microwave-assisted reaction was performed on solid supports without any solvent.[16]

## 4. Experimental

### 4.1. General

All reactions were performed in flame-dried flasks under a nitrogen atmosphere. Benzene, toluene, and 1,3,5-mesitylene were refluxed with sodium and freshly distilled prior to use. Acetonitrile and 1,2-dichloroethane were refluxed with calcium hydride and freshly distilled prior to use. The reaction temperature was controlled carefully with a fine temperature controller in a big water bath with a large amount of water, covered with paraffin oil, and a thick asbestos coating outside the bath within less than ±0.5 °C in the temperature region of 40–90 °C and in a big oil bath with a large amount of oil and a thick asbestos coating outside the bath within less than ±2–3 °C in the temperature region of 100–150 °C. All microwave-assisted reactions were conducted in a commercially available microwave reactor, CEM Discover system™, equipped with an infrared temperature detector. The temperatures were controlled within less than ±1–2 °C in the temperature-controlled microwave-assisted reaction. $^1$H NMR (300 MHz) spectra were recorded in $CDCl_3$ with TMS as an internal standard and chemical shifts are reported in parts per million. *S*-Phenyl 2-diazoethanethioate **1**[8g] and imines **2a–f**[9,17] were prepared according to published procedures. All of the products **3–12** are known compounds and show the identical analytic data to reported data in the literatures.[10,11] The determination of the cis/trans ratios of β-lactam products was performed as reported previously.[10,11]

### 4.2. General procedure for the thermal reactions of *S*-phenyl 2-diazoethanethioate 1a with imine 2

A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) in 1 mL of dry toluene (mesitylene or acetonitrile). The flask was immersed in a water or oil bath, pre-heated, and finely controlled to the desired temperature. A solution of *S*-phenyl 2-diazoethanethioate **1a** (34.7 mg, 0.195 mmol) in 0.5 mL of dry toluene (mesitylene or acetonitrile) was then added via a syringe. The resulting solution was stirred for another 2 h at the same temperature. After removal of the solvent, the residue was directly subjected to NMR analysis to determine the cis/trans ratio of the corresponding *cis*- and *trans*-β-lactam products.

### 4.3. General procedure for the microwave-assisted reactions of *S*-phenyl 2-diazoethanethioate 1a with imine 2

A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) in 1 mL of dry toluene (mesitylene or acetonitrile). The flask was irradiated with microwaves to the desired temperature. A solution of *S*-phenyl 2-diazoethanethioate **1a** (34.7 mg, 0.195 mmol) in 0.5 mL of dry toluene (mesitylene or acetonitrile) was added via a syringe for 2 min. The resulting solution was irradiated for another 20 min at the same temperature. After removal of the solvent, the residue was directly subjected to NMR analysis to determine the cis/trans ratio of *cis*- and *trans*-β-lactam products.

### 4.4. General procedure for the thermal reactions of acyl chlorides 1 with imines 2

A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) and triethylamine (20 mg, 0.195 mmol) in 1 mL of dry toluene (mesitylene or 1,2-dichloroethane). The flask was immersed in a water or oil bath pre-heated and finely controlled to the desired temperature. A solution of the desired acyl chloride **1** (0.195 mmol) in 0.5 mL of dry toluene (mesitylene or 1,2-dichloroethane) was added through a syringe for 2 min. The resulting solution was stirred for another 2 h at the same temperature. The reaction mixture was washed with saturated sodium bicarbonate to remove unreacted acyl chloride and ketene. After drying over sodium sulfate and removal of the solvent, the residue was directly subjected to NMR analysis to determine the cis/trans ratio of *cis*- and *trans*-β-lactam products.

### 4.5. General procedure for the microwave-assisted reactions of acyl chlorides 1 with imines 2

A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) and triethylamine (20 mg, 0.195 mmol) in 1 mL of dry toluene (mesitylene or 1,2-dichloroethane). The flask was irradiated with microwave to the desired temperature. A solution of the desired acyl chloride **1** (0.195 mmol) in 0.5 mL of dry toluene (mesitylene or 1,2-dichloroethane) was added through a syringe for 2 min. The resulting solution was irradiated for another 20 min (1 h for reactions at 60 °C, 15 min for reactions at 150 °C) at the same temperature. The reaction mixture was washed with saturated sodium bicarbonate. After drying over anhydrous sodium sulfate and removal of the solvent, the residue was directly subjected to NMR analysis to determine the cis/trans ratio of *cis*- and *trans*-β-lactam products.

### 4.6. General procedure for the microwave-assisted reactions of acyl chlorides 1 with imines 2 under different microwave irradiation power outputs

A flame-dried round-bottom flask was charged with a solution of imine **2** (0.15 mmol) and triethylamine (20 mg, 0.195 mmol) in 1 mL of dry toluene (mesitylene or benzene). The flask was irradiated with microwaves under the desired power output. After the temperature became stable, a solution of the desired acyl chloride **1** (0.195 mmol) in 0.5 mL of dry toluene (mesitylene or benzene) was added through a syringe for 2 min. The resulting solution was irradiated for another 20 min (1 h for reactions with 10 W power output and 30 min for reactions with 20 W power output) under the same power output. The reaction mixture was washed with saturated sodium bicarbonate. After drying over anhydrous sodium sulfate and removal of the solvent, the residue was directly subjected to NMR analysis to determine the cis/trans ratio of *cis*- and *trans*-β-lactam products.

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