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A Versatile Method for the Synthesis of 3-Alkoxycarbonyl β-Lactam Derivatives

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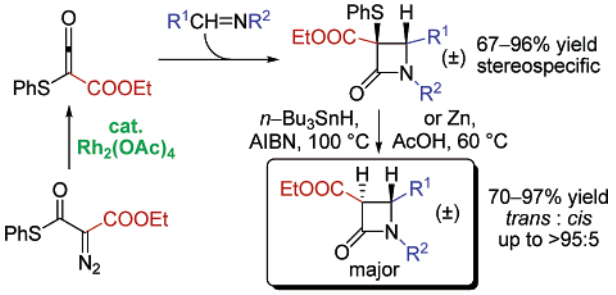

Ketene-imine cycloaddition reactions (the Staudinger reaction) of ethoxycarbonyl(phenylthio)ketene with various imines and subsequent desulfurization reactions were employed to synthesize 3-ethoxycarbonyl β-lactam derivatives. The results indicate that the current approach provides a convenient, mild, and versatile method for synthesizing a variety of 3-alkoxycarbonyl *trans*-β-lactam derivatives with good to excellent yields and diastereoselectivities.

β-Lactam derivatives with various functional groups are important compounds that attract research interests from both synthetic and pharmaceutical fields.[1,2] 3-Alkoxycarbonyl β-lactam derivatives (2-azetidinone-3-carboxylates) are useful synthetic intermediates and building blocks that can be converted to a variety of 3-carbonyl β-lactam derivatives[3] with potential biological activities. A few methods have been developed to synthesize the 3-alkoxycarbonyl β-lactam derivatives, such as the rhodium(II)-[3c,4] or ruthenium(II)-promoted[5] carbene insertion of *N*,*N*-disubstituted 3-alkoxy-2-diazo-3-oxo-propionamides, the manganese(III)-promoted radical cyclization of enamides,[6] and the acidic thermal rearrangement of spiro[cyclopropane-1,5′-isoxazolidine] derivatives.[7] However, the generalities of the published methods are not satisfactory. For instance, the carbene insertion protocol is most frequently used and can achieve the asymmetric synthesis of the 3-alkoxycarbonyl β-lactam derivatives by the use of chiral rhodium(II)[4e] or ruthenium(II)[5] complexes. However, it requires multistep conversions (involving acylation of amine, diazo transfer, and carbene insertion) and is not suitable for substrates bearing other groups sensitive to carbenes. Moreover, in most cases, the yield, regioselectivity, or relative stereoselectivity is poor.[3c,4a,b,d,g,h]

We hope to develop a general and convenient method to prepare the desired 3-alkoxycarbonyl β-lactam derivatives. It is well-known that the ketene-imine cycloaddition reaction (the Staudinger reaction) is one of the most versatile procedures for the synthesis of β-lactam derivatives,[2] in which ketenes were usually generated by the elimination of acyl chlorides. However, alkoxycarbonylketene cannot be directly prepared from alkyl malonyl chloride.[8] The Wolff rearrangement of α-diazocarbonyl compounds is an alternative method to generate ketenes. It was reported that methyl 3-alkylthio-2-diazo-3-oxo-propionate reacted with imines to produce 3-alkylthio-3-methoxycarbonyl β-lactam derivatives[9] and the 3-alkylthio or arylthio group of the β-lactams could be easily removed.[10] Thus, we hope to use ethoxycarbonyl(phenylthio)ketene (**2**), which could be generated from easily prepared ethyl 2-diazo-3-oxo-3-phenylthio-propionate (**1**),[11] as the synthetic equivalent of ethoxycarbonylketene. Herein, a series of 3-ethoxycarbonyl *trans*-β-lactam

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(8) The reaction of ethyl malonyl chloride with *N*-benzylideneaniline in the presence of triethylamine was attempted and failed to afford the desired 3-ethoxycarbonyl β-lactam (For details, see Supporting Information).

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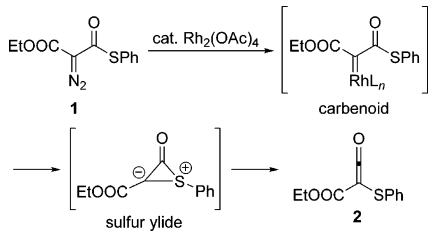
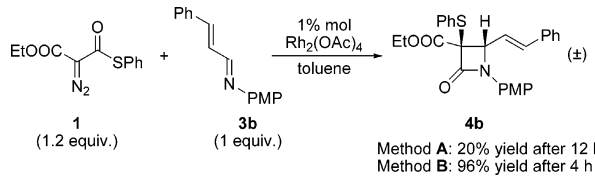
SCHEME 1. $Rh_2(OAc)_4$-Catalyzed Transformation of Diazo Thioester 1 to Ketene 2



SCHEME 2 [a]



[a] PMP = *p*-methoxyphenyl. Method **A**: a solution of diazo thioester **1** in toluene was added to a mixture of $Rh_2(OAc)_4$ and imine **3b** in toluene at 50 °C, and the resulting mixture was stirred for 12 h. Method **B**: a solution of diazo thioester **1** in toluene was added to a suspension of $Rh_2(OAc)_4$ in toluene at 50 °C. After being stirred for 2 h, a solution of imine **3b** in toluene was added to the solution, and then the resulting mixture was stirred for another 2 h.

derivatives were prepared via the Staudinger reaction and a subsequent desulfurization reaction (removal of the phenylthio group) with good to excellent yields and diasteroselectivities. The stereochemistry of the method was investigated as well.

Synthesis of 3-Ethoxycarbonyl-3-phenylthio *β*-Lactam Derivatives. We expected to develop a convenient and mild procedure to synthesize 3-ethoxycarbonyl-3-phenylthio β-lactam derivatives instead of the reported thermal or photoirradiation-induced procedure.[9] Danheiser's group reported that an unsubstituted diazo thioester, *S*-phenyl diazothioacetate, could undergo a thia-Wolff rearrangement to generate phenylthioketene in the presence of $Rh_2(OAc)_4$ catalyst.[12] Nevertheless, for the more complex diazo thioester **1** with an ethoxycarbonyl group attached to its α-position, can it also smoothly rearrange to the desired ketene **2** under the catalysis of $Rh_2(OAc)_4$? It was found that, when the diazo thioester **1** was added to a mixture of $Rh_2(OAc)_4$ and *N*-benzylideneaniline (**3a**) in toluene, the β-lactam product **4a** was obtained in a good yield. This indicated that $Rh_2(OAc)_4$ served as an efficient catalyst to promote the generation of the ketene in a similar way as described by Danheiser et al. (Scheme 1),[12] and the ketene was trapped by the imine to generate the β-lactam product. This also suggests that the $Rh_2(OAc)_4$-promoted thia-Wolff rearrangement is a general route for the generation of phenylthioketene and substituted phenylthioketenes.

However, imine **3b** derived from cinnamaldehyde and *p*-methoxyaniline produced β-lactam **4b** in a very low yield (20%) under the same conditions (Scheme 2, method **A**), and most of diazo thioester **1** was not converted even after 12 h. This suggested that imine **3b** might lower the activity of the catalyst as a result of its coordination to $Rh_2(OAc)_4$ and that method **A** is not suitable for various imines. To avoid the influence of imines, another procedure (Scheme 2, method **B**) was designed and attempted. It was found that, in the presence of $Rh_2(OAc)_4$, diazo thioester **1** was completely converted to ketene **2**, which was stable enough to stand in the toluene solution without dimerization or other side reactions. After the addition of imine **3b**, β-lactam **4b** was obtained in 96% yield, indicating that method **B** is more general than method **A**. Thus, a variety of imines were used as substrates to synthesize the 3-ethoxycarbonyl-3-phenylthio β-lactam derivatives by the use of method **B** (Table 1).

TABLE 1. Scope and Limitation of the Reactions between Diazo Thioester 1 and Imines 3

Entry	Imine	Product [a]	Yield [b] (%)
1	**3a**	**4a**	89
2	**3b**	**4b**	96
3	**3c**	**4c**	85
4	**3d**	**4d**	70
5	**3e**	**4e**	67
6	**3f**	**4f**	71
7	**3g**	**4g**	0 [c]
8	**3h**	**4h**	88
9	**3i**	**4i**	79 [d]

[a] The relative configurations determined by ^{1}H NOE experiments or XRD analysis (see Supporting Information). [b] Isolated yields after column chromatography. [c] Imine **3g** was quantitatively recovered. [d] Reaction is highly diastereoselective producing **4i** as a single racemic diastereomer as reported.[13]

As described in Table 1, most of the imines react well with ketene **2** to produce 3-ethoxycarbonyl-3-phenylthio β-lactam derivatives **4** in good to excellent yields. However, the reaction of ketene **2** with 2-phenyl-2-thiazoline (**3g**) failed to produce β-lactam derivative **4g** (Table 1, entry 7), and the ^{1}H NMR analysis of the reaction mixture revealed no reaction between ketene **2** and imine **3g**.

Considering the stereochemistry, all of the reactions are highly stereoselective, producing products as only a pair of enantiomers. The observed stereochemical results can be rationalized as Scheme 3: (1) For cyclic imines, bicyclic β-lactam products,

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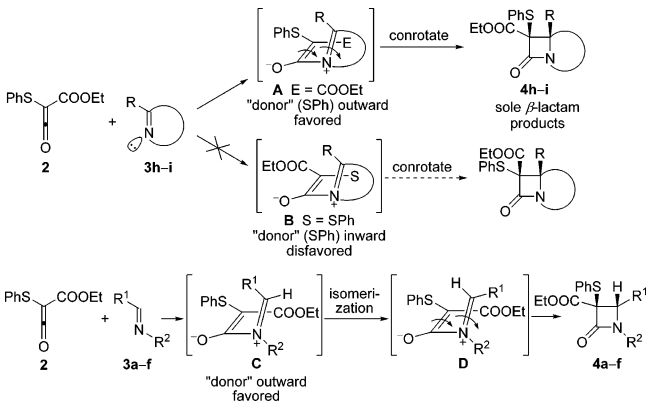
SCHEME 3. Stereochemical Progress of the Reactions between Ketene 2 and Imines 3[a]

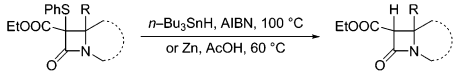


[a] Only one enantiomer is drawn.

of which the imine substituent R is *cis* to the phenylthio group, were exclusively generated. This indicates that imines **3h,i** attack ketene **2** opposite to the phenylthio group to form zwitterionic intermediates **A**. The intermediates **A** subsequently undergo a conrotatory ring closure, with the electronic-donating phenylthio group exclusively occupying the outward position in the ring-closure transition state, to generate the bicyclic β-lactam products **4h,i**. This "donor out" selectivity was subject to the torquoelectronic effect.[14] (2) For acyclic imines, β-lactam products, of which the imine substituent R^1 is *trans* to the phenylthio group, were exclusively generated. Given that the phenylthio group exclusively occupies the outward position in the ring-closure transition state (controlled by the torquoelectronic effect), on the basis of the stereochemistry of the β-lactam products **4a**−**f**, it can be concluded that the corresponding intermediates **C** undergo the C═N double bond isomerization to form intermediates **D**,[2a,15] which generate the β-lactam products **4a**−**f** after a conrotatory ring closure.

Preparation of 3-Ethoxycarbonyl β-Lactam Derivatives: Removal of the Phenylthio Group. Although the removal of the 3-phenylthio group from a β-lactam skeleton has been published (normally employing Raney Ni or *n*-Bu_3SnH/AIBN as reagents),[10] no example has been reported for 3-ethoxycarbonyl-3-phenylthio β-lactam derivatives as starting materials. Since some of our substrates contain other sulfur atoms in addition to the phenylthio group, we did not use the harsh and unselective Raney Ni protocol but used a relatively mild *n*-Bu_3-SnH/AIBN method (Table 2). Meanwhile, considering that the phenylthio group is in the α-position of the ethoxycarbonyl group in our cases, we also attempted Zn/AcOH as reagents,

TABLE 2. Scope and Limitation of the Desulfurization Reactions of β-Lactam Derivatives 4



Entry	Substrate	Product[a]	Product ratio **5** : **6**[b] *n*-Bu_3SnH/AIBN	Product ratio **5** : **6**[b] Zn/AcOH
1	**4a**	(±)–**5a** + (±)–**6a**	88:12 97% yield	84:16 97% yield
2	**4b**	(±)–**5b** + (±)–**6b**	88:12 74% yield	91:9 81% yield
3	**4c**	(±)–**5c** + (±)–**6c**	> 95:5 89% yield	> 95:5 85% yield
4	**4d**	(±)–**5d** + (±)–**6d**	91:9 95% yield	67:33 91% yield
5	**4e**	(±)–**5e** + (±)–**6e**	> 95:5 70% yield	trace[c]
6	**4f**	(±)–**5f** + (±)–**6f**	trace[d]	trace[d]
7	**4h**	(±)–**5h** + (±)–**6h**	no product[e]	75:25 76% yield
8	**4i**	(±)–**5i** + (±)–**6i**	67:33 99% yield	67:33 84% yield

[a] The relative configurations determined by the coupling constants (for **5a**−**f** and **6a**−**f**) or NOE experiments (for **5h,i** and **6h,i**, see Supporting Information). [b] Isolated yields after column chromatography. The product ratios measured by ^{1}H NMR of the crude products. [c] Trace only observed by ^{1}H NMR, and most of the starting material was not converted. [d] Trace only observed by ^{1}H NMR, and most of the starting material became messy. [e] The β-lactam **4h** was thermally unstable and became messy under such conditions (at 100 °C).

which were used in the desulfurization reactions of α-phenylthio esters or ketones,[16] to remove the phenylthio group (Table 2).

The results shown in Table 2 reveal some interesting features about the desulfurization reactions: (1) generally, the two methods can remove the phenylthio group from the β-lactam skeleton in good to excellent yields, but their scopes are slightly different (Table 2, entries 5 and 7); (2) β-lactam, such as **4f**, with more than one carboxylate groups cannot undergo the desulfurization reaction (Table 2, entry 6) and became messy after treatment with the reagents; (3) both desulfurization

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methods are regioselective, removing only the phenylthio group in the α-position of the carbonyl group and do not affect other alkyl or aryl sulfide structures in the substrates (Table 2, entries 7 and 8); and (4) the diastereoselectivities of the two methods are similar, and monocyclic β-lactam derivatives (Table 2, entries 1−5) generally give higher diastereoselectivities than bicyclic β-lactam derivatives (Table 2, entries 7 and 8).

cis-3,4-Disubstituted β-lactams were generally obtained as major products in Raney Ni and *n*-Bu_3SnH/AIBN promoted desulfurizations as a result of hydrogen addition to the less hindered face of the radical intermediates.[10] It is noteworthy that the relative configurations of the predominating 3-ethoxycarbonyl β-lactam products are *trans* isomeric in our cases, which is quite different from those previously reported.[10] Because of the presence of the 3-ethoxycarbonyl group in the substrates, the products possess enolizable centers. Thus, both desulfurization methods lead to the thermodynamically more stable isomers, the *trans*-3,4-disubstituted β-lactams, via a tautomeric equilibrium of the two diastereomers through their enolic intermediates under the reaction conditions.[17] The monocyclic β-lactam derivatives (Table 2, entries 1−5) show diastereoselectivities higher than those of the bicyclic ones due to the more obvious difference in the steric hindrance of hydrogen and aryl or styryl groups than that of the phenyl group and methylene or the sulfur atom.

In summary, a two-step approach involving ketene-imine cycloaddition reactions (the Staudinger reaction) of ethoxycarbonyl(phenylthio)ketene with imines and subsequent desulfurization reactions was used to synthesize various 3-ethoxycarbonyl β-lactam derivatives. The results indicate that the current approach provides a convenient, mild, and versatile method for synthesizing a variety of 3-ethoxycarbonyl *trans*-β-lactam derivatives with good to excellent yields and diastereoselectivities. Otherwise, the uncommon *trans* selectivity of the final products is due to the presence of an enolizable center in the products.

The introduction of the ethoxycarbonyl group to the 3-position of the β-lactam ring is an intriguing process: at the beginning, the phenylthio group plays an important "assistant" role to introduce the ethoxycarbonyl group into the ketene via the $Rh_2(OAc)_4$-promoted thia-Wolff rearrangement; finally, the carboxylate group also plays an important "assistant" role in the diastereoselectivity of the desulfurization reaction. This "double assistant" design may be also useful in bringing other functional groups into the β-lactam skeleton.

Experimental Section

General Procedure for $Rh_2(OAc)_4$-Catalyzed Reactions of Diazo Thioester 1 with Imines 3. A 50-mL three-necked round-bottom flask equipped with a condenser was charged with a suspension of $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol) in 5 mL of toluene. The flask was immersed in an oil bath (50 °C), and a solution of diazo thioester **1** (300 mg, 1.20 mmol) in 5 mL of toluene was added through a dropping funnel during a period of 1 h. After the addition, the reaction mixture was stirred at 50 °C for another 1 h, and a solution of imine **3** (1 mmol) in 5 mL of toluene was added through the dropping funnel. The resulting mixture was stirred for 2 h and was then concentrated. The residue was purified by column chromatography [20 g of silica gel, buffered by 2% Et_3N in ethyl acetate/petroleum ether (60−90 °C) 1:10, gradient elution with ethyl acetate/petroleum ether (60−90 °C), 1:10 to 1:5, v/v] to give the corresponding product **4**.

Ethyl (±)-*trans*-4-(2-Furyl)-1-(4-methoxyphenyl)-2-oxo-3-phenylthioazetidine-3-carboxylate (4c). Colorless crystals, mp 117−118 °C. ^{1}H NMR (300 MHz): δ 1.01 (t, J = 7.2 Hz, 3H), 3.73 (s, 3H), 3.95 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 6.35−6.43 (m, 2H), 6.74−6.77 (m, 2H), 7.11−7.15 (m, 2H), 7.30−7.33 (m, 4H), 7.75 (m, 2H). ^{13}C NMR (75.5 MHz): δ 13.7, 55.3, 59.1, 62.3, 70.0, 110.9, 114.2, 118.7, 128.7, 129.0, 129.6, 130.0, 135.5, 143.6, 146.7, 156.5, 160.2, 165.1. MS (EI) *m*/*z*: 423 (M^+, 4.0), 274 (14), 201 (100), 186 (63). IR ν (cm^{-1}): 1733, 1755. Calcd for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00; N, 3.31. Found: C, 65.27; H, 5.05; N, 3.19.

General Procedure for the Removal of the Phenylthio Group (*n*-Bu_3SnH/AIBN Method). A 50-mL flame-dried three-necked round-bottom flask equipped with a condenser and a rubber stopper was charged with a solution of 3-ethoxycarbonyl-3-phenylthio β-lactam **4** (0.35 mmol) in 5 mL of toluene. The flask was immersed in an oil bath (100 °C), and a solution of *n*-Bu_3SnH (124 mg, 0.42 mmol) and AIBN (6.0 mg, 0.037 mmol) in 3 mL of toluene was added through a syringe during 1 h under stirring. The solution was stirred for another 2 h and then cooled to room temperature. After removal of the solvent, the residue was purified by column chromatography [20 g of silica gel, ethyl acetate/petroleum ether (60−90 °C) 1:10, v/v] to afford the corresponding 3-ethoxycarbonyl β-lactam derivatives **5** and **6**.

General Procedure for Removal of the Phenylthio Group (Zn/AcOH Method). To a solution of 3-ethoxycarbonyl-3-phenylthio β-lactam **4** (0.44 mmol) in AcOH (6 mL) was added zinc powder (372 mg, 5.82 mmol). The reaction mixture was maintained at 60 °C, stirred for 3 h, and then poured into 30 mL of saturated $NaHCO_3$ solution. The mixture was extracted with diethyl ether (15 mL × 3), and the combined organic layer was dried over Na_2SO_4. After the evaporation of the ether, the residue was purified by column chromatography [20 g of silica gel, ethyl acetate/petroleum ether (60−90 °C) 1:10, v/v] to afford the corresponding 3-ethoxycarbonyl β-lactam derivatives **5** and **6**.

Ethyl (±)-*trans*-4-(2-Furyl)-1-(4-Methoxyphenyl)-2-Oxoazetidine-3-Carboxylate (5c). Colorless oil. ^{1}H NMR (300 MHz): δ 1.32 (t, J = 7.2 Hz, 3H), 3.74 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 4.31 (d, J = 2.4 Hz, 1H), 5.34 (d, J = 2.4 Hz, 1H), 6.37−6.39 (m, 1H), 6.53 (d, J = 3.3 Hz, 1H), 6.80−6.84 (m, 2H), 7.27−7.30 (m, 2H), 7.42 (m, 1H). ^{13}C NMR (75.5 MHz): δ 14.1, 50.8, 55.3, 60.2, 62.0, 110.5, 110.6, 114.2, 118.4, 130.6, 143.5, 148.6, 156.4, 158.5, 166.2. MS (EI) *m*/*z*: 315 (M^+, 6.0), 186 (5.5), 166 (6.0), 149 (100). IR ν (cm^{-1}): 1731, 1762. Calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1107.

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Supporting Information Available: Experimental details, additional discussion on the *trans* selectivity in the desulfurization reactions, spectroscopic data for compounds **4** and **5**, the copies of ^{1}H NMR spectra of all unknown compounds, and the crystal structure of **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See Supporting Information for the additional discussion and experiments of *trans* selectivity in the desulfurization reactions.