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Stereodivergent Synthesis of β-Lactams Using Thermal Rearrangement of Aminocyclobutenones

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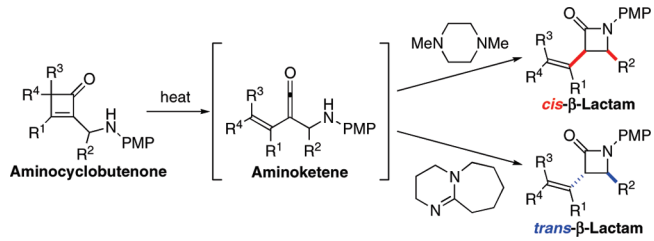
ABSTRACT



In the present study, the stereodivergent synthesis of both *cis*- and *trans*-β-lactams is presented using the following three reactions: iminocyclobutenone formation, chemoselective reduction of imino groups, and thermal rearrangement of aminocyclobutenones as crucial steps, in which the starting materials, iminocyclobutenones, were readily synthesized using conjugate addition reactions of alkynyl imines with ketene silyl acetals in good yields.

New synthetic routes for β-lactams are of great importance because of structure−activity relationship study and the development of new derivatives in the β-lactam antibiotics. It has been recognized that stereochemistry at the C-3 and C-4 carbons of the β-lactam ring is involved in manifestations of biological activity.[1] The Staudinger reaction, the enolate-imine condensations, and the cyclization of β-amino acids or esters have been used for stereocontrolled constructions of the C-3 and C-4 carbons of β-lactams.[2] Although numerous methods for the stereoselective synthesis of *cis*- and *trans*-β-lactams have been reported, a single-step synthesis of them from the same precursor has been highly desired. We have focused on the reactivity at the β-position of alkynyl imines[3] and reported efficient synthetic methods for 2-pyridones, iminopyridines, and aminopyridines using conjugate addition reaction of active methine compounds to alkynyl imines.[4] During these investigations, we envisioned an iminocyclobutenone synthesis by conjugate addition reactions of alkynyl imines with ketene silyl acetals. Iminocyclobutenones would be useful intermediates for the synthesis of nitrogen-containing heterocycles by transformation including the thermal rearrangement of the cyclobutenone ring.[5] This paper describes the stereodivergent synthesis of both *cis*- and *trans*-β-lactams **8** using iminocyclobutenone **3** formation, chemoselective reduction of imino groups, and thermal rearrangement of aminocyclobutenones **4** as crucial steps (Scheme 1).

We first examined the aluminum chloride promoted conjugate addition reaction of several alkynyl imines **1** with ketene silyl acetals **2**.[6] Table 1 summarizes the results. The alkynyl imines possessing heteroaromatic or aromatic groups as the substituent R^2 underwent conjugate addition reactions

(1) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3.

(2) For a review on the synthesis of β-lactams, see: Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

(3) For a review on the alkynyl imines in organic synthesis, see: Stadnichuk, M. D.; Khramchikhin, A. V.; Piterskaya, Yu. L.; Suvorova, I. V. *Russ. J. Gen. Chem.* **1999**, *69*, 593.

(4) Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Commun.* **2009**, 874.

(5) For a recent example of thermal rearrangement of cyclobutenones, see: Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 425.

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Scheme 1. Proposed Transformation of Iminocyclobutenones **3** into β-Lactams **8**

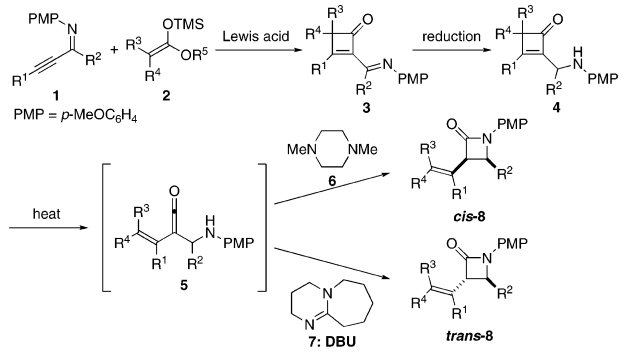
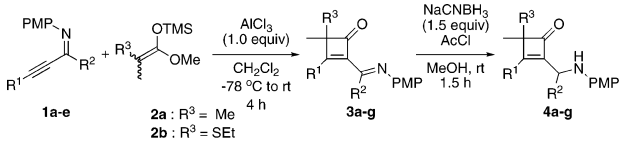


Table 1. Synthesis of Imino- and Aminocyclobutenones



entry	R^{1a}	R^{2a}	imine	R^3	**3** (yield %)[b]	**4** (yield %)[b]
1	Ph	Ph	**1a**	Me	**3a** (82[c], 71[d])	**4a** (95[e])
2	Ph	2-furyl	**1b**	Me	**3b** (85[c], 75[d])	**4b** (67[f])
3	Ph	Np	**1c**	Me	**3c** (80[c], 77[d])	**4c** (79[e])
4	Ph	2-thienyl	**1d**	Me	**3d** (71[d])	**4d** (78[e])
5	Np	Ph	**1e**	Me	**3e** (75[c])	**4e** (90[g])
6	Ph	Ph	**1a**	SEt	**3f** (78[c])	**4f** (89[e,h])
7	Ph	Np	**1c**	SEt	**3g** (83[c])	**4g** (84[e,h])

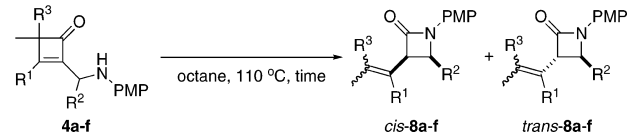
[a] Np = 2-naphthyl. [b] Isolated yields. [c] Ketene silyl acetals **2a** and **2b** (3.0 equiv) were used. [d] Ketene silyl acetal **2a** (1.5 equiv) was used. [e] AcCl (1.5 equiv) was used. [f] AcCl (0.5 equiv) was used. [g] AcCl (1.0 equiv) was used. [h] Diastereomeric ratio was 1/1.

to give the corresponding iminocyclobutenones **3a**−**d** in good to high yields (entries 1−4).[7] Use of 1.5 equiv of **2a** slightly decreased the yields (entries 1−3). The reaction of alkynyl imines **1a** and **1c** with the ketene silyl acetal **2b** having an ethanesulfenyl group gave iminocyclobutenones **3f** and **3g** in good yields (entries 6 and 7).

We next examined chemoselective reduction of iminocyclobutenones **3** having three reducible functional groups such as imino, carbonyl, and alkenyl. When sodium cyanoborohydride was used as a reducing reagent, the reduction of iminocyclobutenones **3a**−**g** in methanol in the presence of acetyl chloride, which reacted with methanol to generate a limited amount of hydrogen chloride in situ, proceeded chemoselectively at room temperature to give the desired aminocyclobutenones **4a**−**g** in moderate to high yields (Table 1).

Thermal rearrangement of aminocyclobutenones **4a**−**f** in toluene or octane at 110 °C proceeded to give the desired β-lactams **8a**−**f** in moderate to good yields with good *cis*-selectivities.[8] Table 2 summarizes the results.[9]

Table 2. Thermal Rearrangement of Aminocyclobutenones into β-Lactams

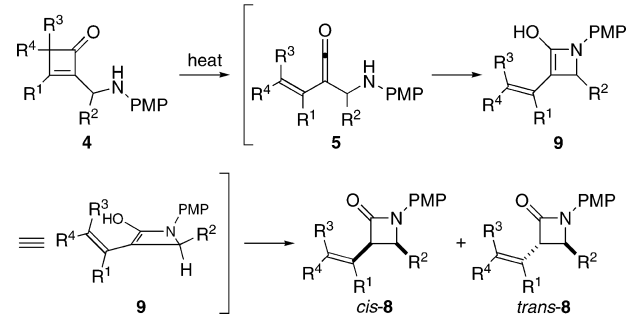


entry	R^{1a}	R^{2a}	R^3	time (h)	**8** (yield %)[b]	*cis*/*trans*[c]
1[d]	Ph	Ph	Me	24	**8a** (61)	80/20
2	Ph	2-furyl	Me	45	**8b** (76)	74/26
3	Ph	Np	Me	40	**8c** (69)	75/25
4	Ph	2-thienyl	Me	48	**8d** (89)	79/21
5	Np	Ph	Me	48	**8e** (51)	79/21
6	Ph	Ph	SEt	48	**8f** (65)	80/20[e]

[a] Np = 2-naphthyl. [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR spectra. [d] Reaction performed in toluene. [e] A geometrical mixture of the double bond.

A plausible reaction mechanism for the thermal rearrangement of aminocyclobutenones **4** into β-lactams **8** is shown in Scheme 2. Aminoketene **5** would be generated by ring

Scheme 2. Plausible Mechanism for the Thermal Rearrangement



opening of aminocyclobutenone **4** and undergo a cyclization to give the enol intermediate **9**. Protonation of the enol intermediate **9** would occur from the less hindered face of the enol to give *cis*-β-lactam **8** predominantly. The protonation step is crucial regarding the *cis*-selectivity. Therefore, several additives were investigated in the thermal rearrangement of aminocyclobutenones **4c** to improve the *cis*-selectivity, and Table 3 summarizes the results. We first examined several amines as a proton transfer additive.[10]

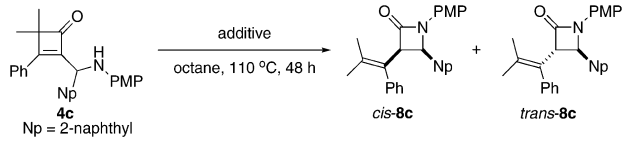
(6) The reactions using other Lewis acids such as $TiCl_4$, $ZrCl_4$, and $EtAlCl_2$ gave the iminocyclobutenone in yields ranging from 8% to 25%.

(7) The reaction of an alkynyl imine **1** possessing an aliphatic group as the substituent R^1 (R^1 = ^{n}Bu, R^2 = Ph) gave the δ-lactam instead of the β-lactam.

(8) Relative stereochemistry at C(3) −C(4) was determined on the basis of the $J_{3,4}$; coupling constants for *cis*-β-lactams are larger than those for *trans*-isomers. See: Bouffard, F. A.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1130.

(9) Among the solvents examined, such as toluene, xylene, octane, and chlorobenzene, octane was found to be the most effective.

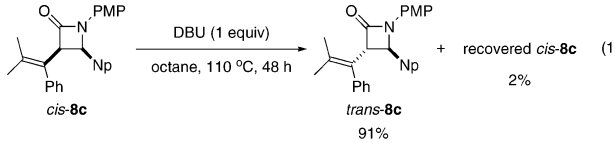
Table 3. Effect of Additive in the Thermal Rearrangement



entry	additive[a]	equiv	**8c** (yield%)[b]	*cis*/*trans*[c]
1	none		69	75/25
2	proton sponge	1.0	71	89/11
3	DABCO	1.0	99	83/17
4	*N*-methylmorpholine	1.0	61	83/17
5	1,4-dimethylpiperazine (**6**)	1.0	98	94/6
6	**6**	2.0	93	97/3
7	**6**	3.0	90	97/3
8	1,4-diethylpiperazine	1.0	93	97/3
9	DBN	1.0	31	33/67
10	DBU (**7**)	1.0	59	2/98
11	**7**	0.5	67	30/70
12	**7**	0.2	98	54/46
13	BHT	1.0	41	79/21

[a] BHT = 2,6-di-*tert*-butyl-4-methylphenol. [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR spectra.

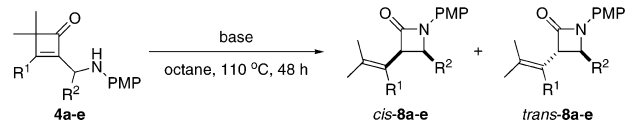
Among the amines tested, 1,4-dimethylpiperazine (**6**) and 1,4-diethylpiperazine were found to be the most effective regarding both the *cis*-selectivity and the yield (entries 1−8).[11] On the other hand, thermal rearrangement in the presence of stronger bases such as DBN and DBU (**7**) gave the β-lactam **8c** with *trans*-selectivity (entries 9 and 10). When isomerization of *cis*-β-lactam **8c** into the *trans*-counterpart **8c** was examined in octane with DBU (**7**), *trans*-β-lactam **8c** was obtained in 91% yield along with the recovered *cis*-β-lactam **8c** in 2% yield (eq 1). Use of a substoichiometric amount of DBU (**7**) did not give good *trans*-selectivities (entries 11 and 12). These results suggest that *cis*-β-lactam **8c** would be kinetically produced and then isomerize into the thermodynamically more stable *trans* β-lactam **8c**. Use of 2,6-di-*tert*-butyl-4-methylphennol (BHT) as an acidic additive was not effective (entry 13).



We next examined a diastereoselective synthesis of a variety of β-lactams, and the results are summarized in Table 4. Whereas use of 1,4-dimethylpiperazine (**6**) gave β-lactams **8a**−**e** in good to high yields with good to high *cis*-selectivities (entries 1−5), DBU (**7**) effected formation of their *trans*-counterparts **8a**−**e** in moderate to good yields with excellent selectivities (entries 6−10).

In conclusion, we found that the thermal rearrangement of aminocyclobutenones in the presence of an appropriate amine produced either *cis*- or *trans*-β-lactams with high selectivities. β-Lactams are the most important nitrogen-containing compounds because of their biological activities[12] as well as their use as versatile building blocks.[13] The present method offers an attractive alternative β-lactam synthesis because aminocyclobutenones can be easily prepared from readily available starting materials.

Table 4. Diastereoselective Synthesis of β-Lactams by Thermal Rearrangement of Aminocyclobutenones



entry	base[a]	R^{1b}	R^{2b}	**8** (yield%)[c]	*cis*/*trans*[d]
1[e]	**6**	Ph	Ph	**8a** (80)	98/2
2	**6**	Ph	2-furyl	**8b** (99)	82/18
3	**6**	Ph	Np	**8c** (93)	97/3
4	**6**	Ph	2-thienyl	**8d** (77)	94/6
5	**6**	Np	Ph	**8e** (85)	95/5
6[e]	**7**	Ph	Ph	**8a** (78)	3/97
7	**7**	Ph	2-furyl	**8b** (80)	2/98
8	**7**	Ph	Np	**8c** (59)	2/98
9	**7**	Ph	2-thienyl	**8d** (59)	2/98
10	**7**	Np	Ph	**8e** (75)	3/97

[a] 1,4-Dimethylpiperazine (**6**) (2.0 equiv) or DBU (**7**) (1.0 equiv) was used. [b] Np = 2-naphthyl. [c] Isolated yields. [d] Diastereomeric ratios were determined by ^{1}H NMR spectra. [e] Reaction performed in toluene.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research (B) and Priority Areas from MEXT and JSPS.

Supporting Information Available: Experimental procedures and product characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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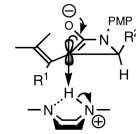
(10) Tang reported that an appropriate amine was essential in the Kinugasa reaction to control both diastereo- and enantioselectivities, in which the amine might coordinate to the copper and relay the chirality to the product; see: Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576. For a similar aminoketene intermediate, see: Ahn, C.; Kennington, J. W., Jr.; DeShong, P. *J. Org. Chem.* **1994**, *59*, 6282. Fu indicated that the Kinugasa reaction would proceed through ring-opening fragmentation to a ketene, followed by recyclization, where the role of the amine was thought to be both deprotonation of an acetylene with copper catalyst to generate the copper acetylide and protonation of the enolate; see: Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082.

(11) Regarding the role of 1,4-dimethylpiperazine (**6**), we presume the formation of a bulky proton source shown.



(12) For a review on the biological activity of β-lactams, see: von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072.

(13) For a review on the β-lactam synthon method, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.