HETEROCYCLES, Vol. 66, 2005, pp. 75 – 80. © The Japan Institute of Heterocyclic Chemistry
Received, 24th August, 2005, Accepted, 20th October, 2005, Published online, 21st October, 2005. COM-05-S(K)24

A CATION-EXCHANGE RESIN PROMOTED IMINO ALDOL REACTION OF CHIRAL ALKOXYKETENE SILYL ACETALS WITH α,β-UNSATURATED IMINES, LEADING TO A FACILE SYNTHESIS OF β-LACTAMS

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Abstract – Imino aldol reaction of chiral ketene silyl acetals derived from 3-hydroxybutanoates with α,β-unsaturated imines proceeds smoothly to give β-amino esters in good yields with high *syn*-selectivity under the influence of a cation-exchange resin. Subsequent treatment with *tert*-butylmagnesium chloride gave β-lactams in a highly stereoselective manner.

We have been interested in the stereoselective synthesis of β-lactams using the imine (**1**) possessing a chiral auxiliary derived from (2*S*,3*S*)-tartaric acid,[1] since β-lactam antibiotics still constitute one of the most widely utilized classes of drugs due to their highly therapeutic index in humans.[2] Our continuous interests in the stereodivergent construction of the β-lactam rings with or without substituent at 3-position led us to examine the preparation of 3-alkoxy-β-lactams in a highly stereoselective manner and disclosed a conveninent ruoute to a key intermediate for the synthesis of 2-isocephem (**4**) and 2-oxa-isocephem (**5**) β-lactam antibiotics (eq. 1).[3] During these investigations cation-exchange resins have been found to be excellent activators for imino aldol reaction of ketene silyl acetals with imines, which, after cyclization, would to lead to the stereoselective synthesis of β-lactams. Use of ion-exchange resins offers several advantages in organic synthesis, *e.g*. simplification of reaction procedures, easy separation of products without discharging harmful waste water, repeated use, and so on. In our previous report, a cation-exchange resin, in particular Amberlyst® 15 DRY, having a large surface area (45 m^2/g), was found to be one of the most useful resins that promoted imino aldol type reaction, where the addition reactions proceeded with high chemoselectivity in the presence of two kinds of imines and/or

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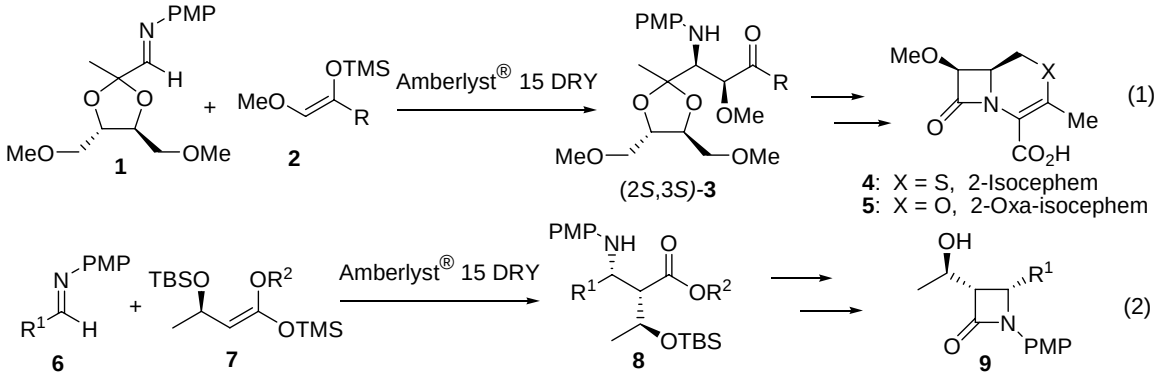
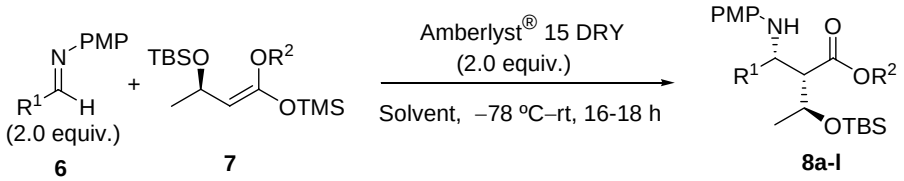
This paper is dedicated to the memory of Professor Kenji Koga.

nucleophiles.[4] Many of β-lactam antibiotis possess a chiral hydroxyethyl substituent at the 3-position, and construction of such β-lactam ring systems has received considerable attention. We would like to report a facile construction of β-lactam ring possessing a chiral hydroxyethyl substituent at its 3-position using stereoselctive imino aldol reaction promoted by a cation-exchange regin as a crucial step (eq. 2).



Imino aldol reaction of the chiral ketne silyl acetal (**7**) with a variety of imines (**6**) was carried out in an effort to find the most effective substituent at the imino carbon, and Table 1 summarizes the result.

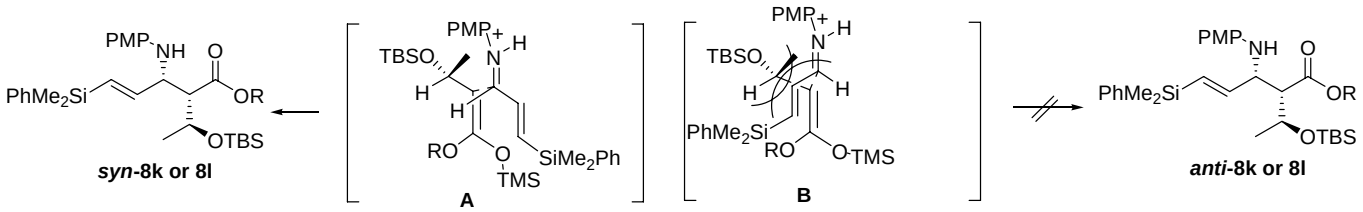
Table 1. Reaction of the Chiral Ketene Silyl Acetal (**7**) with Imine (**6**) in the Presence of Amberlyst® 15 DRY[a]



Entry	R^1	R^2	Solvent	**8**/%[b]	*syn*:*anti* [c]	de (*syn*)/%[c]
1	MeO_2C	OMe	CH_2Cl_2	**a**: 77	52:48	28
2	EtO_2C	OMe	CH_2Cl_2	**b**: 78	53:47	26
3	*i*-PrO_2C	OMe	CH_2Cl_2	**c**: 76	54:46	31
4	TBSC≡C	OMe	CH_2Cl_2	**d**: 0[d]	-	-
5	TESC≡C	OMe	CH_2Cl_2	**e**: 0[d]	-	-
6	HC≡C	OMe	CH_2Cl_2	**f**: 0[d]	-	-
7	2-Thienyl	OMe	CH_2Cl_2	**g**: 62	98: 2	100
8	2-Furyl[e]	OMe	CH_2Cl_2	**h**: 49	98: 2	100
9	(*E*)-TBSCH=CH	OMe	CH_2Cl_2	**i**: 64	97: 3	100
10	(*E*)-TBSCH=CH	OMe	EtOH	**i**: 44	88:12	100
11	(*E*)-TMSCH=CH	OMe	CH_2Cl_2	**j**: 70	96: 4	100
12	(*E*)-TMSCH=CH	OMe	EtOH	**j**: 40	86:14	100
13	(*E*)-$PhMe_2SiCH$=CH	OMe	CH_2Cl_2	**k**: 82	97: 3	100
14	(*E*)-$PhMe_2SiCH$=CH	OEt	CH_2Cl_2	**l**: 49	99: 1	100
15	(*E*)-$PhMe_2SiCH$=CH[f]	OEt	CH_2Cl_2	**l**: 68	99: 1	100

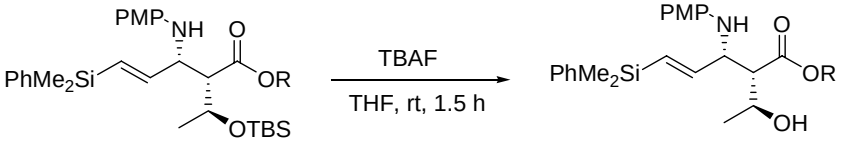
[a]Reaction was carried out according to the typical procedure (Ref. 5). [b]Isolated yield. [c]Determined by ^{1}H NMR and/or HPLC. [d]Hydrolyzed aldehyde derived from the imine (**6**) was obtained.. [e]**6** : **7** : Amberlyst = 2.5 : 1.0 : 2.5. [f]**6** : **7** : Amberlyst = 2.0 : 2.0 : 1.0.

As shown in Table 1, use of the imines derived from glyoxylates gave the adducts with low stereoselectivities, whereas desired adducts were not obtained using acetylene derivatives (Entries 1~ 6). Use of α,β-unsaturated imines recorded good to excellent *syn*-selectivities, where the diastereomeric exccesses were usually very high (Entries 7 ~ 15). Regarding the solvent, use of ethanol decreased both the product yields and selectivities (Entries 8 and 10). In terms of product yield and diastereoselctivity, phenyldimethylsilylethenyl derivatives were chosen as the acceptor (Entries 11, 14, and 15). This high *syn*-selectivity is most reasonably explained in terms of the non-chelated acyclic transition state (**A**) as depicted in Scheme 1, where a less sterically congested transitionstate (**A**) leads to *syn*-adducts.



Scheme 1.

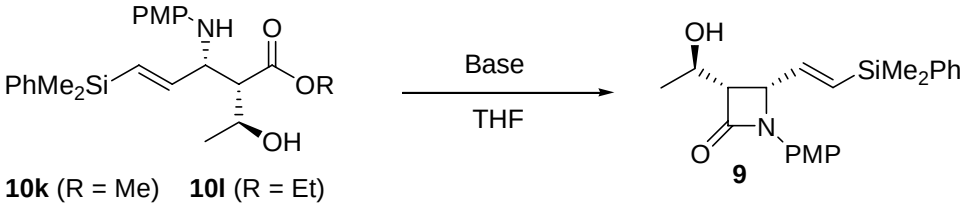
We next examined the cyclization to β-lactams. However, the use of the adducts (**8**) for cyclization under basic conditions did not give the β-lactams in good yileds, presumably due to the steric bulk of the TBS group, and therefore, we next examined the desilylation of TBS group and the subsequent cyclization.



Scheme 2.

Upon treatment of the compound (**8k**) or (**8l**) with TBAF desilylation of the TBS group proceeded smoothly to give the alcohol (**10k)** or (**10l**) in good yield (Scheme 2). Subsequent treatment of the desilylated β-amino ester (**10**) with *i*-PrMgCl gave the desired β-lactam (**9**) in moderate yields with concomitant epimerization of the hydroxyethyl group at the C-3 position of the β-lactam ring (Table 2, Entries 1 ~ 3), whereas the use of *t*-BuMgCl proved to be superior in terms of product yields and diastereoselectivity (Entries 4 ~ 9). The best result was obtained using 2.5 equivalents of *t*-BuMgCl at 55 ^{o}C, and in this case no epimerization was observed (Entry 7). When the ethyl ester was used, recovery of the starting material was observed under essentially the same cyclization conditions (Entry 9).

Table 2. Cyclization of Amino Ester (**10**) into β-Lactam (**9**).[a]



10k (R = Me) **10l** (R = Et) **9**

Entry	**10**	Base (eq.)	Temp. / °C	Time/h	**9**/%[b]	*cis* : *trans*[c]
1	**k**	*i*-PrMgCl (2.0)	rt	2.0	21	91: 9
2	**k**	*i*-PrMgCl (2.0)	rt	18.0	34	84:16
3	**k**	*i*-PrMgCl (2.5)	55	2.5	44	75:25
4	**k**	*t*-BuMgCl (2.0)	rt	18.0	16	100: 0
5	**k**	*t*-BuMgCl (2.0)	55	2.0	34	100: 0
6	**k**	*t*-BuMgCl (2.0)	55	19.0	43	100: 0
7	**k**	*t*-BuMgCl (2.5)	55	3.0	79[d]	100: 0
8	**k**	*t*-BuMgCl (3.0)	55	17.0	69	75:25
9	**l**	*t*-BuMgCl (2.5)	55	3.0	62[e]	100: 0

[a]Reaction was carried out according to the typical procedure (Ref. 6). [b]Isolated yield. [c]Determined by ^{1}H NMR and/or HPLC. [d]The starting material (**10k**) was recovered in 7% yield. [e]Recovery of (**10l**) in 14%.

For further elaboration of the β-lactam (**9**) obtained in a stereoselective manner, we carried out several functional group transformations. Removal of the PMP group was readily carried out using ceric ammonium nitrate as an oxidant in MeCN/H_2O at –15 to 10 °C to give the β-lactam (**11**) in 75% yield. Desilylation of the vinylsilane moiety was conducted with TBAF in THF at 40 °C to give the desilylated β-lactam (**12**) in 73% yield. Isomerization into the *trans*-β-lactam (**13**) was effected by treating of **11**with I_2 in refluxing benzene. However, the yields of **13** were in the range of 32 to 40%, and improvement of this process is currently under investigation to achieve the synthesis of 1β-methylcarbapenem derivatives (**14**).[7]

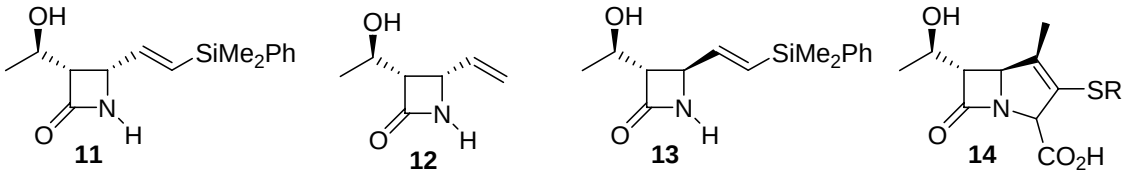


Figure 1.

In conclusion, we have found that the imino aldol reaction was promoted by a cation-exchange resin to give the adduct, β-amino ester in good yields with high *syn*-selectiviy. Using chiral ketne silyl acetals derived from (3*R*)-hydroxybutyrates, highly stereoselective formation of *cis*-β-lactams was achieved after cyclization of the initially formend *syn*-β-amino esters with *t*-BuMgCl. These processes offer a

stereoselective approach to 3-hydroxyethylated β-lactams whih are important synthetic intermediated for many of β-lactam antibiotics of potentially high activity.

REFERENCES AND NOTES

1. (a) T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron Lett.*, 1991, **32**, 7563. (b) T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron*, 1992, **48**, 5629. (c) M. Shimizu, Y. Ukaji, J. Tanizaki, and T. Fujisawa, *Chem. Lett*., 1992, 1349. (d) T. Fujisawa, R. Hayakawa, and M. Shimizu, *Tetrahedron Lett.,* 1992, **33**, 7903. (e) T. Fujisawa, K. Higuchi, and M. Shimizu, *Synlett*, 1993, 59. (f) T. Fujisawa, M. Ichikawa, Y. Ukaji, and M. Shimizu, *Tetrahedron Lett.*, 1993, **34**, 1307. (g) T. Fujisawa, D. Satou, and M. Shimizu, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2343. (h) M. Shimizu, T. Ishida and T. Fujisawa, *Chem. Lett*. 1994, 1403**.**
2. (a) W. Durckheimer, J. Blumback, R. Lattrell, and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl*., 1985, **24**, 180. (b) "Chemistry and Biology of β-Lactam Antibiotics," ed. by R. B. Morin and M. Gorman, Academic Press, New York, 1982, Vol. 1-3. (c) T. Kametani, K. Fukumoto, and M. Ihara, *Heterocycles*, 1982, **17**, 463.
3. M. Shimizu, M. Tachi, and I. Hachiya, *Chem. Lett*., 2004, **33**, 1394.
4. (a) M. Shimizu and S. Itohara, *Synlett*, 2000, 1828. (b) M. Shimizu, S. Itohara, and E. Hase, *Chem. Comm*., 2001, 2318.
5. A typical experimental procedure for the imino aldol reaction is as follows: To a suspension of Amberlyst 15 DRY(215.0 mg, 1.00 mmol on the sulfonic acid portion, washed EtOH and dried in vacuo at 100 ^{o}C) and the imine (**6**) (R^1 = (*E*)-$PhMe_2SiCH=CH$) (295.4 mg, 1.00 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of ketene silyl acetal (**7**) (R^2= Me, 152.3 mg, 0.50 mmol) in CH_2Cl_2 (3.0 mL) at –78 ^{o}C under an argon atmosphere. After being stirred at –78 ^{o}C for 2 h, the reaction mixture was allowed to stand at room temperature for 12 h. The suspension was filtered through a Celite pad. The filtrate was concentrated in vacuo to afford a crude oil. Purification on preparative silica gel TLC (*n*-Hex / EtOAc = 10 / 1, as an eluent, developed twice) gave the adduct (**8k**) (219.0 mg, 82%) as a pale yellow oil. Examination by HPLC indicated the formation of diastereomers in a 96:4 (*syn*:*anti*) ratio and 100% de for the *syn*-isomer. ^{1}H-NMR(270 MHz, $CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.29 (s, 3H), 0.30 (s, 3H), 0.90 (s, 9H), 1.22 (d, *J* = 5.9 Hz, 3H), 2.78 (dd, *J* = 5.3 and 8.3 Hz, 1H), 3.57 (s, 3H), 3.73 (s, 3H), 3.91 (br s, 1H), 4.28 (dq, *J* = 5.9 and 8.3 Hz, 1H), 4.42-4.45 (m, 1H), 6.04-6.07(m, 2H), 6.55-6.62 (m, 2H), 6.73-6.77 (m, 2H), 7.28-7.32 (m, 3H), 7.41-7.44 (m, 2H). IR ($CHCl_3$) 3392, 2953, 2857, 1737, 1617, 1513, 1467, 1375, 1248, 1111, 1042, 987, 897, 832, 777, 733, 700, 471 cm^{-1}.
6. A typical experimental procedure for the cyclization into β-lactam as follows: To a solution of the

amino ester (**10k**) (471.8 mg, 0.91 mmol) in THF (1.0 mL) was added *t*-BuMgCl (2.90 mL, 2.85 mmol, 0.98 M in THF) at room temperature, and the mixture was stirred at 55 ^{o}C for 3.0 h. H_2O (1.0 mL) was added to quench the reaction, and the whole mixture was extracted with EtOAc (5 mL x 3). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to give a crude oil, which was purified on preparative silica gel TLC (*n*-Hex / EtOAc = 2 / 1, as an eluent) to give the β-lactam (**9**) (273.0 mg, 79%) as a pale yellow oil together with the recovered amino ester (**10k**) (27.1 mg, 7%). β-lactam (**9**): ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.37(s, 6H), 1.41 (d, *J* = 6.1 Hz, 3H), 3.40 (dd, *J* = 5.5 and 9.8 Hz, 1H), 3.79 (s, 3H), 4.15 (dq, *J* = 6.1 and 9.8 Hz, 1H), 4.65 (ddd, *J* = 1.8, 3.7 and 5.5 and Hz, 1H), 6.34-6.35 (m, 2H), 6.82-6.84 (m, 2H), 7.30-7.38 (m, 5H), 7.46-7.47 (m, 2H). IR ($CHCl_3$) 3447, 2958, 1739, 1512, 1248, 1114, 1036, 950, 830, 470cm^{-1}.

7. (a) T. Fujisawa, R. Hayakawa, and M. Shimizu, *Chem. Lett*., 1995, 1013. (b) R. Hayakawa, I. Fuseya, T. Konagaya, M. Shimizu, and T. Fujisawa, *Chem. Lett*., 1998, 49.