A Cation-exchange Resin Promoted Imino Aldol Reaction, Leading to the Synthesis of 2-Isocephem and 2-Oxa-isocephem

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Imino aldol reaction of ketene silyl acetals with the chiral imine **1** proceeds smoothly to give β-amino esters in good yields with high diasetereoselectivity under the influence of a cation-exchange resin, and the subsequent functional group transformations provide a formal synthesis of 2-isocephem and 2-oxa-isocephem β-lactam antibiotics.

β-Lactam antibiotics still constitute one of the most widely utilized classes of drugs due to their highly therapeutic index in humans.[1] For the synthesis of such a class of compounds one of the most straightforward approaches involves the ester enolate-imine condensation. However, stereocontrolled construction of both the C-3 and C-4 carbons does not appear to be trivial. Our continuous interests in the stereodivergent construction of the β-lactam rings with or without substituent at 3-position[2] led us to examine the preparation of 3-alkoxy-β-lactams in a highly stereoselective manner. 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 lead to the stereodivergent 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 nucleophiles.[3]

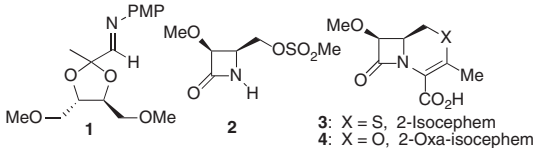
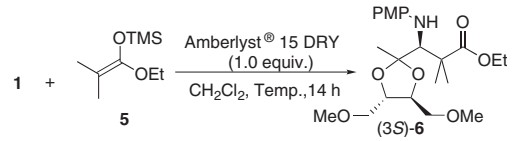


Figure 1.

In connection with the recent interest in the semi-synthesis of taxol[4] as well as potentiality as a versatile synthon for the synthesis of various important β-lactam antibiotics such as 2-isocephem,[5] 2-oxa-isocephem,[5] 7-methoxycephalosporin,[6] and PS-5,[7] a stereodivergent synthesis of β-lactams possessing an alkoxy group at the 3-position is one of the most useful applications using the imino aldol reaction promoted by a cation-exchange resin. Previous studies have already revealed the versatility of the chiral imine **1** for the ester enolate-imine condensation method of β-lactam synthesis.[2] In the present paper we would like to disclose a stereoselective synthesis of 3-alkoxy-β-lactams by the ester enolate-imine condensation promoted by a cation-exchange resin using the chiral imine **1**, and application to the synthesis of a key intermediate **2** for 2-isocephem (**3**) and 2-oxa-isocephem (**4**).

The starting chiral imine **1** was prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in 3 steps.[2b] The reaction of the ketene silyl acetal **5** was initially used for the optimization of the addition reaction, and Table 1 summarizes the results.

Table 1. Reaction of **5** with the chiral imine **1** in the presence of Amberlyst® 15 DRY[a]



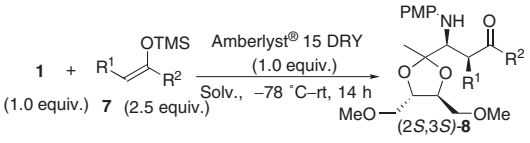
Entry	**5**/equiv.	Temp./°C	**6**/%[b]	3*S*:3*R*
1	1.2	rt	11	97:3
2	1.2	−78–rt	32	97:3
3	2.5	−78–rt	76	94:6
4	3.0	−78–rt	69	94:6

[a]Carried out according to the typical procedure (Ref. 8). [b]Isolated yield.

As shown in Table 1, when the reaction was carried out with 1.2 equiv. of **5** at room temperature, the desired adduct **6** was obtained in low yield, where a concomitant hydrolysis of the ketene silyl acetal was observed to some extent. The best yield was obtained when the reaction was conducted with 2.5 equiv. of **5** at −78 °C–room temperature. Under these conditions a variety of ketene silyl acetals were subjected to the addition reaction, and Table 2 summarizes the results.

As shown in Table 2, the addition in methanol or ethanol

Table 2. Reaction of ketene silyl acetal **7** with the chiral imine **1** in the presence of Amberlyst® 15 DRY[a]



Entry	R^1	R^2	Solvent	**8**/%[b]	*syn*:*anti*[c]	de (*syn*)/%[c]
1	OMe	OMe	EtOH	21	ND[d]	ND[d]
2	OMe	OMe	MeOH	22	ND[d]	ND[d]
3	OMe	OMe	*i*-PrOH	82	73:27	61
4	OMe	OMe	CH_2Cl_2	97	95:5	96
5	OTBDMS	OMe	CH_2Cl_2	90	99:1	86
6	OTBDMS	OMe	*i*-PrOH	88	99:1	14
7	NBn_2	OMe	CH_2Cl_2	0	—:—	—
8	Et	S-*t*-Bu	CH_2Cl_2	trace	ND[d]	ND[d]

[a]Carried out according to the typical procedure (Ref. 8). [b]Isolated yield. [c]Determined by ^{1}H NMR and/or HPLC. [d]Not determined.

gave the adduct in poor yield, whereas the reaction gave the adduct in good yield when *i*-propyl alcohol was used as a solvent (Entries 1–3). The best product yield and diastereoselectivity were obtained when the reaction was run in dichloromethane, where *syn*-adduct **8a** ($R^1 = R^2 =$ MeO) was formed in good diasteromeric excess (Entry 4). Excellent yields and *syn*-selectivities were observed with the TBDMSO derivative **7b**, although the diasetereomeric excess of the *syn*-isomer was modest (Entry 5). However, the addition did not proceed with the ketene silyl acetal derived from a glycine derivative (Entry 7). Ketene silyl thio acetal was not employable due to the competing hydrolysis under the reaction conditions (Entry 8). The addition product **8a** (*syn*:*anti* = 95:5) was readily transformed into the β-lactam **9** in 93% yield on treatment with *i*-PrMgCl in THF, and each isomer was readily separated on silica gel TLC. Examination of the coupling constant unambiguously established the relative stereochemistry.[9] On the basis of the diastereoselectivity, the following transition state was proposed. The chiral imine **1** was protonated with the cation-exchange resin, and the ketene silyl acetal approached from the sterically less hindered face in an *anti*-periplaner fashion to give the (2*S*,3*S*)-adduct **8a** as a major product. (Figure 2)

Transformation into a key intermediate for the synthesis of 2-isocephem and 2-oxa-isocephem was readily carried out as shown in Scheme 1. First, the chiral auxiliary was removed on treatment with TfOH in refluxing 2-butanone, and the resulting methyl ketone **10** was silylated with TMSOTf/Et_3N to give the silyl enol ether **11** in quantitative yield. The silyl enol ether

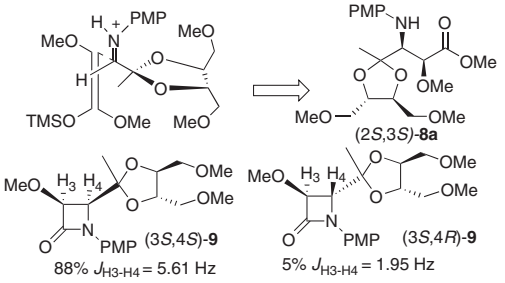
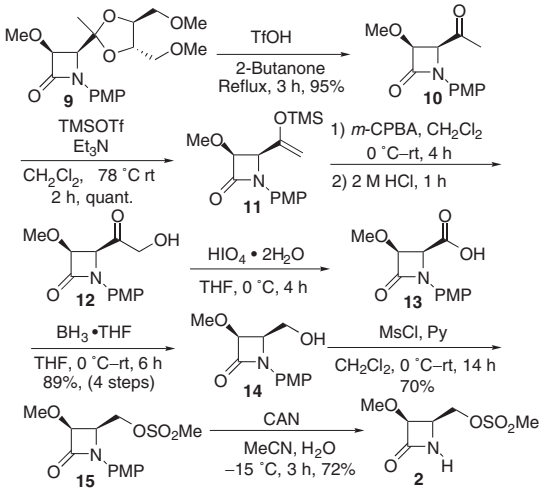


Figure 2.



Scheme 1.

11 was transformed into the primary alcohol **14** via the following four step sequences in excellent overall yield of 89% (*m*-CPBA oxidation, HCl treatment, cleavage with HIO_4, and reduction with BH_3•THF). Mesylation followed by removal of the PMP group with CAN gave the known key intermediate **2**[5,10] to **3** and **4**.

In conclusion, we have developed an efficient method for the synthesis of β-lactams substituted at the C-3 and C-4 positions in a *cis*-orientation using a cation-exchange resin promoted imino aldol reaction. Using this methodology, an easy approach was developed to a key intermediate for the synthesis of 2-isocephem and 2-oxa-isocephem.

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8 A typical experimental procedure is as follows: To a suspension of Amberlyst 15 DRY(43.0 mg, 0.2 mmol on the sulfonic acid portion, washed EtOH and dried in vacuo at 100 °C) and the imine **1** (61.9 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of ketene silyl acetal **7a** ($R^1 = R^2 =$ MeO, 96.2 mg, 0.5 mmol) in CH_2Cl_2 (5.0 mL) at −78 °C under an argon atmosphere. After being stirred at −78 °C for 2 h, the reaction mixture was allowed to stand at room temperature for 12 h. The suspension was filtrated through a Celite pad. The filtrate was concentrated in vacuo to afford a crude oil. Purification on preparative silica gel TLC (*n*-Hex / Et_2O = 1/3, as an eluent, developed twice) gave the adduct **8a** (80.2 mg, 97%) as a pale yellow oil. Examination by HPLC indicated the formation of diastereomers in a 95:5 (*syn*:*anti*) ratio and 96% de for the *syn*-**8a**.

9 Determination of the absolute stereochemistry, see Ref. 2h.

10 **2**: Yellow oil; $[\alpha]_D^{23.2}$ −130.2 (*c* 0.013, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.06 (s, 3H), 3.57 (s, 3H), 4.07–4.13 (m, 1H), 4.34 (dd, J = 11.2, 7.92 Hz, 1H), 4.46 (dd, J = 11.2, 4.29 Hz, 1H), 4.63–4.66 (m, 1H), 6.24 (brs, 1H); IR ($CHCl_3$): 3187, 3015, 1722, 1457, 1344, 1194, 1168, 990, 968, 826 cm^{-1}; MS (ESI): m/z 210 $(M + H)^+$.

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