HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 203 - 208. © The Japan Institute of Heterocyclic Chemistry
Received, 18th March, 2008, Accepted, 24th April, 2008, Published online, 28th April, 2008. COM-08-S(N)43

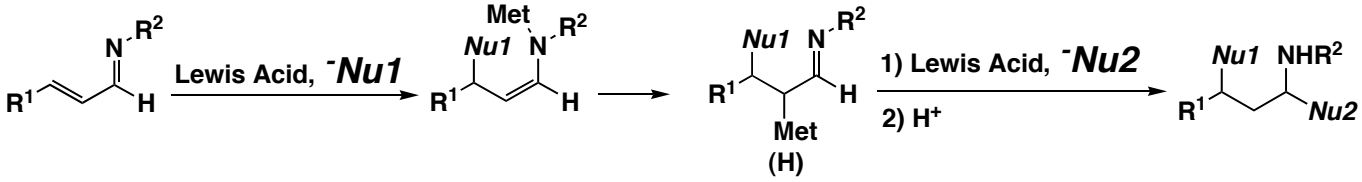
REGIOSELECTIVE DOUBLE NUCLEOPHILIC ADDITION REACTION LEADING TO THE SYNTHESIS OF β-LACTAMS

Atsushi Takahashi, Shiho Kawai, Iwao Hachiya, and Makoto Shimizu*

Department of Chemistry for Materials, Graduate School of Engineering Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp

Abstract – β-Lactams were prepared in a regio- and stereoselective manner using the double nucleophilic addition of ketene silyl acetals and ketene silyl thioacetals to α,β-unsaturated imines followed by base-promoted cyclization. An attempted approach to 2-aryl carbapenem is also described.

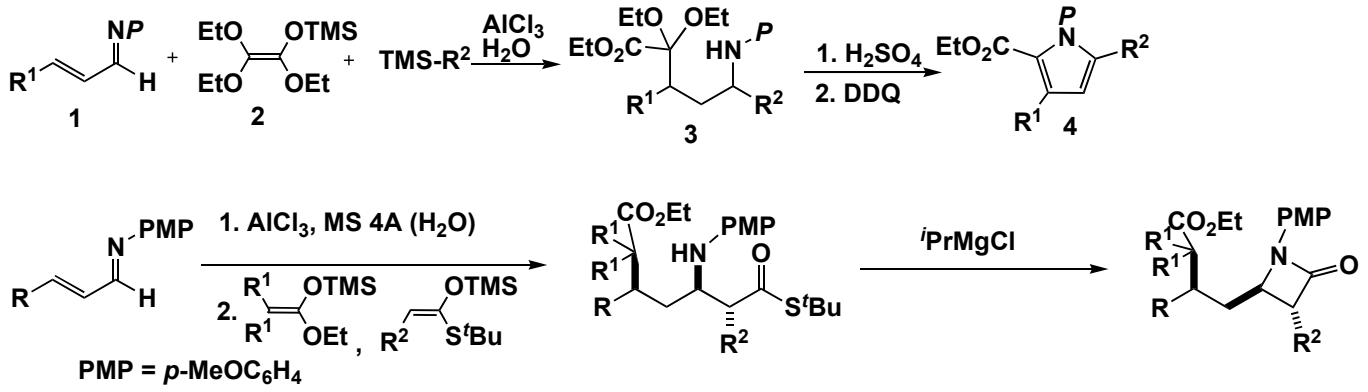
We have already found that in the presence of an appropriate Lewis acid, a mixture of two different nucleophiles reacts with α,β-unsaturated aldimines to give double addition products in a regioselective manner in good yields, *i. e.*, ketene silyl acetals and their thio analogues undergo 1,4- and 1,2-additions, respectively.[1] This approach avoids unnecessary isolation processes of relatively unstable imino intermediates[2] to give amino esters in good yields.



Scheme 1

When dialkoxy ketene silyl acetal (**2**), an acyl anion equivalent, is used as the first nucleophile, this methodology offers a facile synthetic route to a γ-amino carbonyl synthon (**3**), which in turn is transformed into 2,3,5-trisubstituted pyrrole (**4**).[3] Further examination into the use of the adducts arising from the addition of ketene silyl acetals as the first nucleophiles and ketene silyl thioacetals as the second ones led to a facile synthesis of β-lactams in a regioselective manner. This paper reports these reactions in detail.

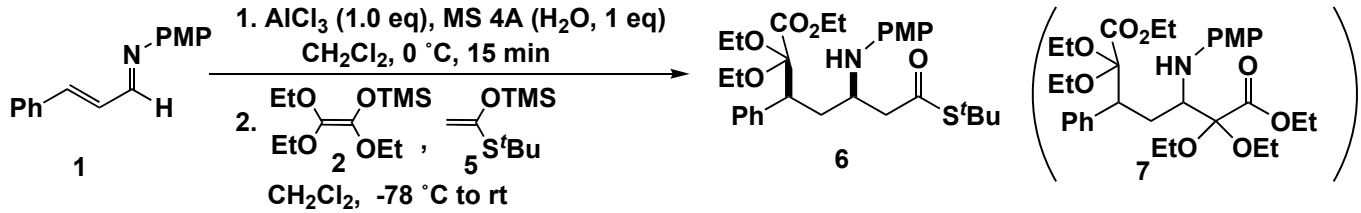
This paper is dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday.



Scheme 2

The initial examination was carried out to find optimum double nucleophilc addition conditions using the addition of the diethoxy ketene silyl acetal (**2**) and ketene silyl thioacetal (**5**) to α,β-unsaturated aldimine (**1**). Table 1 summarizes the results.

Table 1. Double Nucleophilic Addition to the α,β-Unsaturated Aldimine (**1**) under Various Conditions[a]



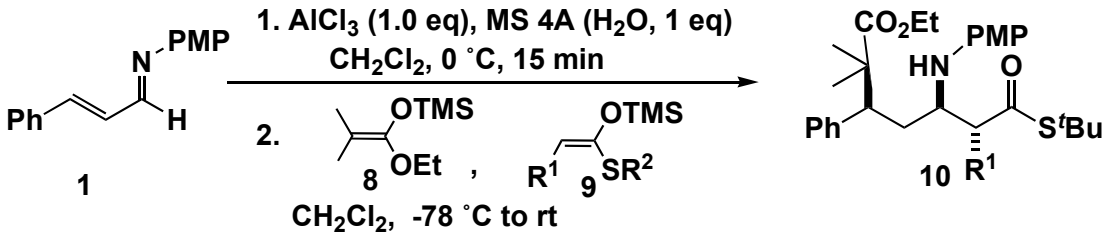
Entry	**2** (equiv)	**5** (equiv)	Time (h)	**6**/%[b]	*syn* : *anti* of **6**[c]	**7**/%[b]
1	1.0	1.5	14.0	59	83 : 17	10
2	1.0	2.0	11.5	58	95 : 5	5
3	1.1	1.5	14.0	65	92 : 8	10
4	1.1	2.0	12.0	76	89 : 11	5
5	1.3	1.7	11.5	80	90 : 10	7
6	1.3	2.0	14.0	63	93 : 7	23
7	1.5	1.5	9.5	58	81 : 19	16
8	1.5	2.0	11.5	70	92 : 8	4

[a]Reaction was carried out at -78 °C to rt according to the typical procedure (Ref. 4). [b]Isolated yield. [c]Determined by ^{1}H NMR and/or HPLC.

In all the cases examined, the reaction proceeded in a regioselective manner to give the adduct (**6**) as a major product in good yields with *syn*-selectivity. The best yield of the double addition product was

obtained when **2** (1.3 equiv) and **5** (1.7 equiv) were used, where the by-product (**7**) was formed in 7% yield (Entry 5). Under these conditions several ketene silyl thioacetels were subjected to the addition reaction to the imine (**1**), and Table 2 summarizes the results.

Table 2. Double Nucleophilic Addition to the α,β-Unsaturates Aldimine (**1**)[a]

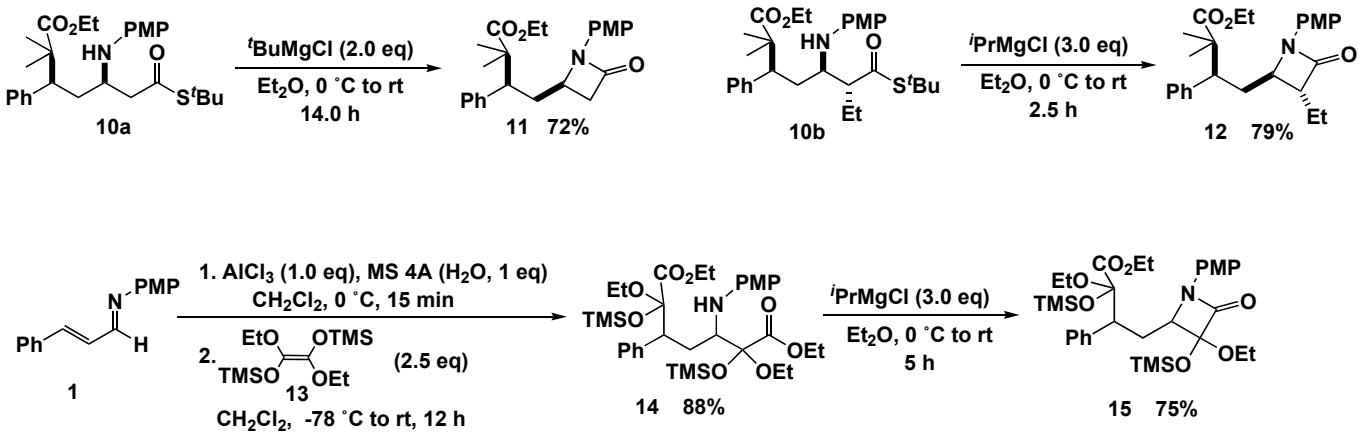


Entry	R^1	R^2	Time (h)	**10**/%[b]	Diastereomer Ratio[c]
1	H	^{t}Bu	12.0	79	>99 (*syn*) : 1 (*anti*)
2	Et	^{t}Bu	12.5	42	92 : 8 : 0 : 0
3	Et	Et	11.5	81	82 : 13 : 5 : 0
4	OTBS	^{t}Bu	11.0	59	52 : 42 : 6 : 0

[a]Reaction was carried out according to the typical procedure (Ref. 4). [b]Isolated yield. [c]Determined by ^{1}H NMR and/or HPLC.

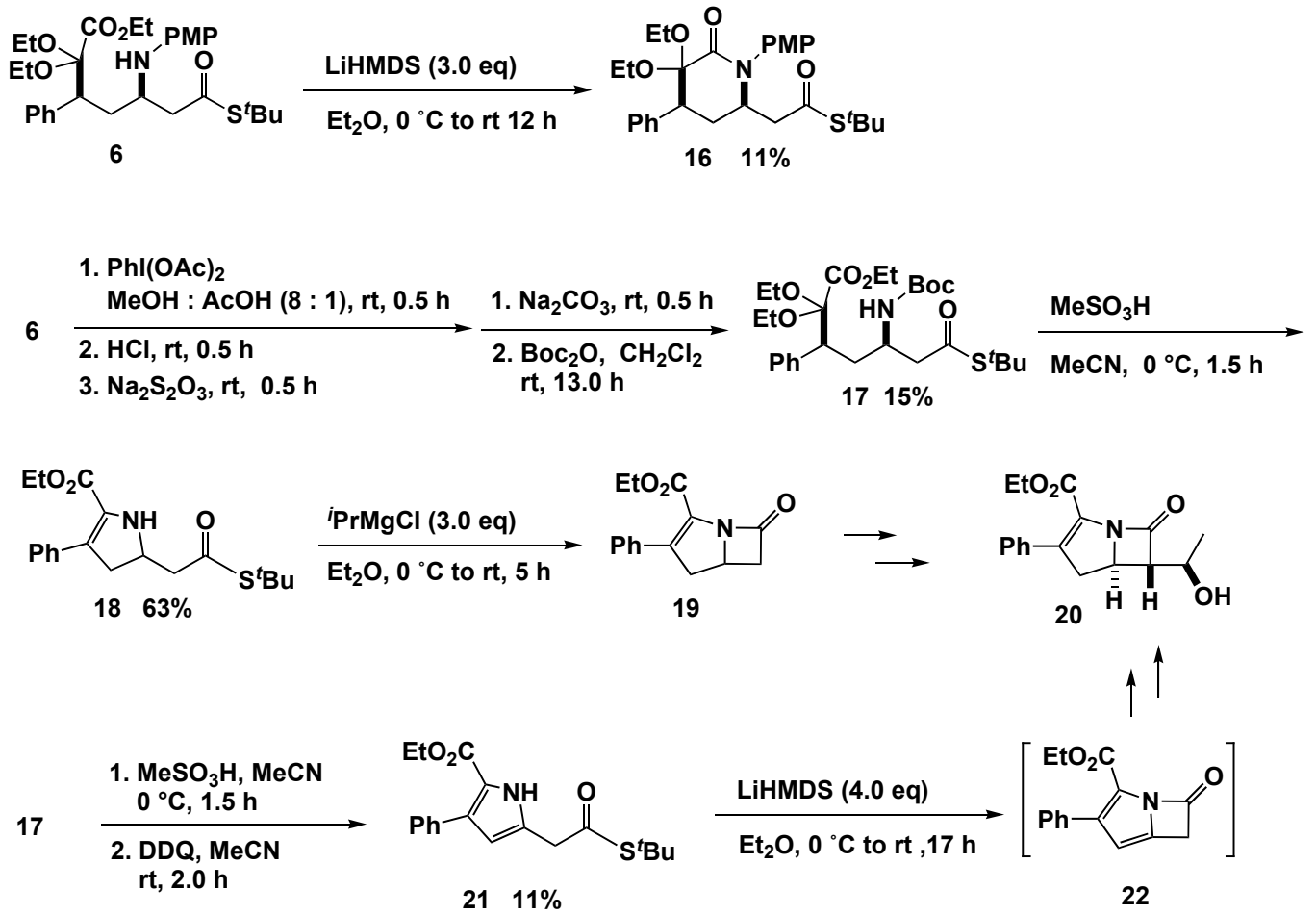
When disubstituted ketene silyl *tert*-butylthioacetal was used, the reaction gave the adduct (**10**) in a regioselective manner in good yield with high *syn*-selectivity (Entry 1), whereas trisubstitued analogues gave moderate yields of the adducts (Entries 2 and 4). Although diastereoselectivity was somewhat lost, the yield was improved using the ethylthio derivative (Entry 3).

We next examined cyclization of the adducts into β-lactams under various conditions. Among the bases examined (^{t}BuMgCl, ^{i}PrMgCl, LiHMDS, and NaHMDS), the use of ^{t}BuMgCl, ^{i}PrMgCl, and LiHMDS gave satisfactory results.[5]



Scheme 3

In particular, a single diastereomer (**12**)[6] was obtained starting from the adduct (**10b**) under these cyclization conditions. Use of the ketene silyl acetal (**13**) as the first and the second nucleophiles led to the formation of the β-lactam (**15**) possessing protected ketones as a mixture of several diastereomers. This class of β-lactam may be used for the synthesis of 2-aryl carbapenem derivatives of which we are actively exploring an efficient synthesis.[7] For this purpose, the transformation of the adduct (**6**) (see, Table 1) into β-lactam was also attempted.



Scheme 4

Under several basic conditions, however, the adduct (**6**) did not give β-lactam, and instead, δ-lactam (**16**) was always formed in low yield. We then turned our attention, first, to construct the dihydropyrrole ring. The PMP protecting group was removed with $PhI(OAc)_2$ followed by Boc protection to give **17** in 15% overall yield. Cyclization was effected with $MeSO_3H$ to give the dihydropyrrolle (**18**) in 63% yield.[3] However, an attempted cyclization into 2-phenyl carbapenem (**19**) only gave a trace amount of the desired compound. In contrast to the dihydropyrrole (**18**), the pyrrole (**21**) prepared by the cyclization–DDQ oxidation of **17** underwent cyclization into an unstable bicyclic β-lactam (**22**) in low

yield (<22%). We are currently investigating appropriate cyclization conditions for **18** and transformation methods via **22** to synthesize 2-aryl carbapenems of biological interest.[7]

In conclusion, we have found that a double nucleophilic addition to α,β-unsaturated aldimines offers a useful method for the synthesis of β-lactams using two different nucleophiles (ketene silyl acetals and their thio analogues), where the regio- and diastereoselectivies are noteworthy.

REFERENCES AND NOTES

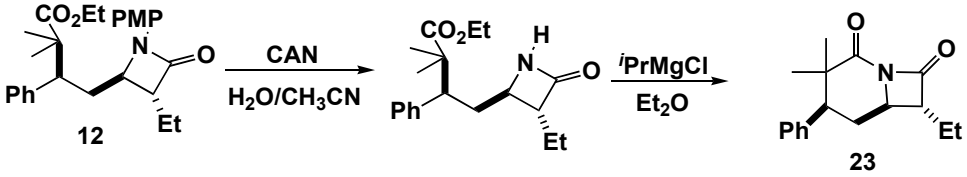
1. M. Shimizu, M. Kamiya, and I. Hachiya, *Chem. Lett.*, 2005, **34**, 1456, and earlier references cited therein.
2. M. D. Stadnichuk, A. V. Khramchikhin, Y. L. Piterskaya, and I. V. Suvorova, *Russ. J. Gen. Chem.*, 1999, **69**, 593.
3. M. Shimizu, A. Takahashi, and S. Kawai, *Org. Lett.*, 2006, **8**, 3585.
4. Typical experimental procedure for the double nucleophilic addition is as follows: Under an argon atmosphere, a suspension of $AlCl_3$ (26.7 mg, 0.20 mmol) and Molecular Sieves 4A containing H_2O (1 eq) in CH_2Cl_2 (2.0 mL) were stirred at 0 °C for 15 min. To the resulting solution was added a solution of *N*-*p*-methoxyphenylcinnamylidenamine (**1**) (47.6 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) at -78 °C, and the mixture was stirred for 10 min. A solution of 1-ethoxy-2-methyl-1-trimethylsiloxypropene (**8**) (48.3 mg, 0.26 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture. After stirring for 5 min, a solution of 1-*tert*-butylthiotrimetylsiloxyetene (**9a**) (61.7 mg, 0.30 mmol) in CH_2Cl_2 (1.0 mL) was added to the resulting mixture. The mixture was gradually warmed to rt during 12.0 h. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (10 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a crude product. Purification on silica gel TLC (toluene : EtOAc = 40 : 1 as an eluent, developed three times) gave the adduct (**10a**) (76.9 mg, 79 %). Rf = 0.21 (*n*-hexane/AcOEt = 7 : 1); light pink oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.01 (s, 3H), 1.15 (s, 3H), 1.21-1.27 (m, 3H), 1.41 (s, 9H), 1.55-1.60 (m, 1H), 2.17-2.23 (m, 1H), 2.37 (dd, *J* = 7.3, 14.4 Hz, 1H), 2.59 (dd, *J* = 4.3, 14.4 Hz, 1H), 3.06-3.39 (m, 3H including a double doublet at 3.38 ppm, *J* = 2.2, 12.2 Hz, 1H), 3.70 (s, 3H), 4.08-4.19 (m, 2H), 6.32-6.35 (m, 2H), 6.66-6.68 (m, 2H), 7.10-7.12 (m, 2H), 7.21-7.28 (m, 3H).

   Cyclization into β-lactam (**12**): To a solution of the adduct (**10a**) (66.5 mg, 0.137 mmol) in Et_2O (4.0 mL) was added a THF solution of *tert*-butylmagnesium chloride (0.54 M, 0.51 mL, 0.275 mmol) at 0 °C, and with stirring the whole mixture was gradually warmed to rt during 14.0 h. Saturated aqueous NaCl (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (10 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a crude product.

Purification on silica gel TLC (*n*-hexane : EtOAc = 7 : 1 as an eluent, developed twice) gave β-lactam (**11**) (39.1 mg, 72 %) as a single isomer. Rf = 0.21 (*n*-hexane/AcOEt = 7 : 1); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (s, 3H), 1.16 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 2.02-2.09 (m, 1H), 2.24 (dd, *J* = 1.8, 15.3 Hz, 1H), 2.29-2.32 (m, 1H), 2.68 (dd, *J* = 5.2, 15.3 Hz, 1H), 3.12 (dd, *J* = 2.5, 11.0 Hz, 1H), 3.79 (s, 3H), 3.86-3.93 (m, 1H), 4.07-4.16 (m, 2H), 6.83-6.86 (m, 2H), 7.16-7.29 (m, 7H).

5. (a) E. J. Corey, C. P. Decicco, and R. C. Newbold, *Tetrahedron Lett*., 1991, **32**, 5287. (b) M. Shimizu, M. Tachi, and I. Hachiya, *Chem. Lett*., 2004, **33**, 1394. (c) M. Shimizu, M. Tachi, S. Fukushima, and I. Hachiya, *Heterocycles*, 2005, **66**, 75. (d) M. Shimizu, Y. Hayashi, R. Hamanaka, and I. Hachiya, *Heterocycles*, 2007, **73**, 191.

6. The relative stereochemistry of the β-lactam (**12**) was determined by transforming into the bicyclic lactam (**23**), and examination of the coupling constants in the ^{1}H-NMR spectrum established the relative stereochemistry.



7. D. H. Shi, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, 1984, **21**, 29; N. Yasuda, L. Xavier, D. L. Rieger, Y. Li, A. E. DeCamp, and U.-H. Dolling, *Tetrahedron Lett.,* 1993, **34**, 3211; R. Hayakawa, I. Fuseya, T. Konagaya, M. Shimizu, and T. Fujisawa, *Chem. Lett*., 1998, 49; M. A. Huffman and N. Yasuda, *Synlett*, 1999, 471.