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NOVEL METHOD FOR THE SYNTHESIS OF β-LACTAMS BY THE REACTION OF α-BROMOCARBOXYLIC ACIDS WITH IMINES MEDIATED BY TRIPHENYLPHOSPHINE

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Abstract – The useful and simple method for the formation of the β-lactams by the reaction between α-bromo carboxylic acids and imines is described. This reaction was effectively mediated by triphenylphosphine or polystyryl-diphenylphosphine to give the β-lactams in good yields with high *trans*-selectivity.

β-Lactams are one of the most important heterocycles in medicinal chemistry as skeletons of antibiotics, such as penicillins, cephalosporins and carbapenems *etc*.[1] Therefore, until now, many useful methods for constructing β-lactam rings were developed and the numerous articles and accounts have been published.[2]

For example, the Staudinger reaction is one of the most versatile means to get β-lactams, which is a [2+2] cycloaddition between imines and ketenes.[2a, c] Moreover, it is known that the cyclization of the β-amino acid derivatives is one of the other useful means. This reaction is convenient to get both *trans*- and *cis*-isomers, because the stereochemistry of β-lactams depends upon the β-amino acid derivatives that can be synthesized diastereoselectively.[2b, c]

In recent years, we have been interested in the study of the reaction using phosphines and have already reported that several reactions were promoted by the combination of phosphine and Lewis acid effectively.[3] For example, it has been already reported that the Reformatsky-type reaction of α-bromo

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carbonyl compounds was mediated by the (*o*-tolyl)$_3$P/TiCl$_4$ combination in good yields with high diastereoselectivity.[3b, c] In addition, it was also found that these composite reagents smoothly promoted the Mannich-type reaction of the α-bromo thioesters with imines.[3f]

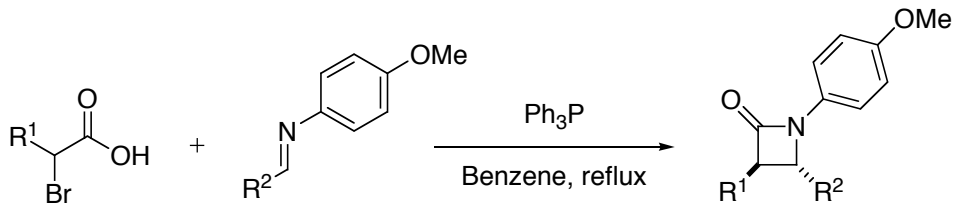
This time, we found that the β-lactams were formed by the reaction between α-bromo carboxylic acids and imines in the presence of triphenylphosphine. Thus, in this manuscript, we would like to describe the convenient method for the synthesis of β-lactams with *trans*-selectivity in one step.

Initially, we examined the reaction of 2-bromo-2-phenylacetic acid with *N*-(4-chlorobenzylidene)-*p*-anisidine in benzene at 70 °C using various phosphines, such as tributylphosphine, tri-*o*-tolylphosphine, triphenylphosphine and so on. Then it was found that the desired β-lactam, 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-phenyl-2-azetidinone, was obtained with *trans*-selectivity in any cases and that triphenylphosphine was the best promoter of this reaction among phosphines examined.

Next, we investigated the effects of solvents, such as MeCN, THF, DMF, toluene and benzene, in the same reaction using triphenylphosphine. The desired β-lactam was obtained in moderate yield (30%-67%) in any solvents and among solvents examined, the highest yield was achieved in benzene. Moreover, it was found that the reaction proceeded more smoothly under benzene reflux condition.[4]

Then, under the optimized reaction conditions,[5] the reaction of 2-bromoacetic acid derivatives with

Table 1.[a] The reaction of α-bromocarboxylic acids with several imines under the optimized conditions.



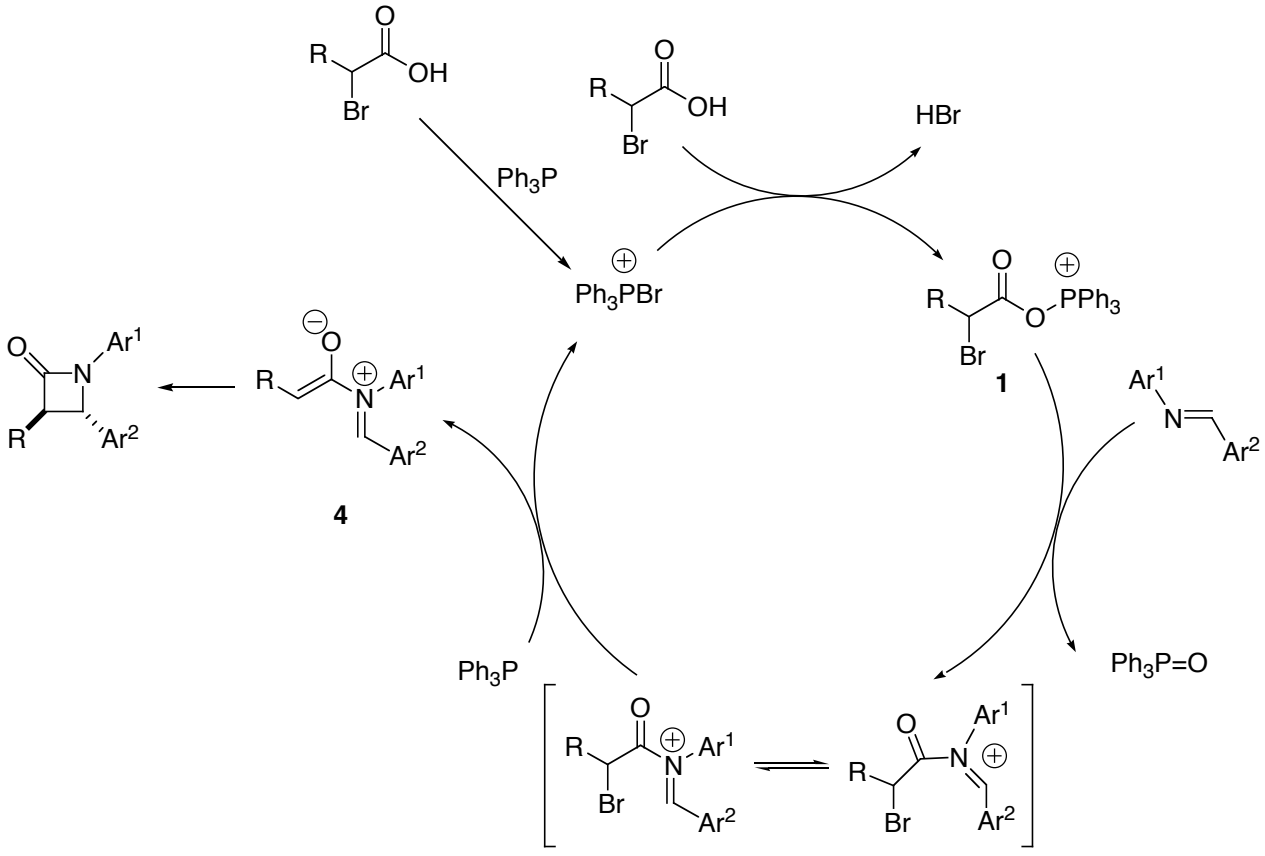
Entry	R^1	R^2	Time (h)	Yield (%) [b]	*trans* : *cis* [c]
1	Ph	*p*-MeOC$_6$H$_4$	24	82	100 : 0
2	Ph	Ph	18	98	95 : 5
3	Ph	*p*-ClC$_6$H$_4$	12	100	91 : 9
4	Ph	*p*-NO$_2$C$_6$H$_4$	12	100	88 : 12
5	Ph	PhCH=CH$_2$	12	27	100 : 0
6	*p*-BrC$_6$H$_4$S	*p*-ClC$_6$H$_4$	12	93	85 : 15
7	Me	*p*-ClC$_6$H$_4$	24	26	79 : 21

[a] Molar ratio of acid:imine:Ph$_3$P=1.2:1.0:2.4. [b] Isolated yield. [c] The stereochemistry of these products was assigned by the vicinal coupling constants of C3 and C4 protons: *trans*-Isomers; 1.8-2.6 Hz. *cis*-Isomers; 6.0-6.5 Hz.

several imines was carried out. The results are summarized in Table 1.

As can be seen from Table 1, the reaction of 2-bromo-2-phenylacetic acid and imines derived from aromatic aldehydes proceeded in high yields with good *trans*-selectivity (Entries 1-4). Moreover, it should be noted that when the imine had an electron-donating group on the 4-position of aldehyde moiety, the diastereoselectivity of the product became higher and that an electron-withdrawing group, in contrast, made the yield higher. Although the yield was low in the reaction with the imine derived from cinnamaldehyde, it was confirmed that the corresponding β-lactam was obtained as a single *trans*-isomer (Entry 5). Moreover, the reaction of 2-bromo-2-(4-bromophenylthio)acetic acid[6] with *N*-(4-chlorobenzylidene)-*p*-anisidine proceeded in good yield with high *trans*-selectivity (Entry 6). In addition, the reaction of 2-bromopropionic acid (Entry 7) was also achieved with *trans*-selectivity. However, in this case, both the yield and the stereoselectivity were lower.

The mechanism of this reaction was thought as follows; first, a little amount of α-bromo carboxylic acid reacted with triphenylphosphine to give triphenylphosphonium bromide. Next, this triphenyl-phosphonium bromide reacted with other α-bromo carboxylic acid and the compound (**1**), which had a good leaving group, was formed. Then, the reaction of this compound (**1**) with imines proceeded in the presence of triphenylphosphine and the corresponding β-lactam was obtained through the formation of the intermediate (**3**).[7] The substituent on the 4-position of aldehyde moiety had an effect on the rate of

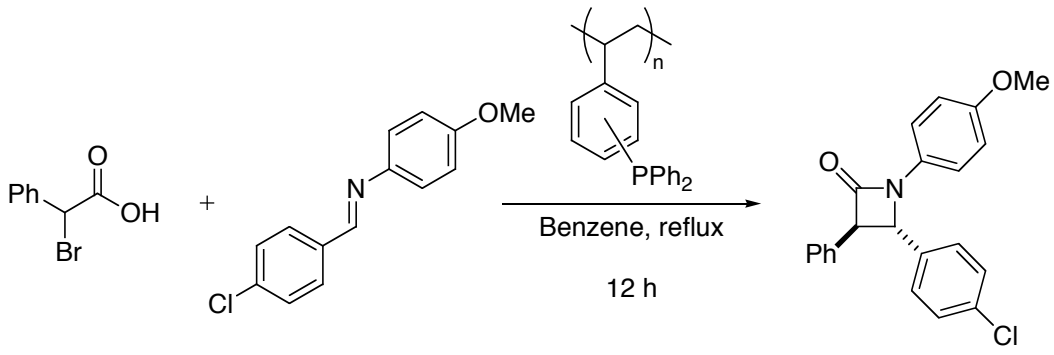


Scheme 1

the isomerization between (**2**) and (**3**); that is, the electron-donating group made the rate faster.

A typical procedure for the synthesis of 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-phenyl-2-azetidinone (Entry 1) is as follows: Under an argon atmosphere, a benzene (4 mL) solution of *N*-(4-chlorobenzylidene)-*p*-anisidine (51.5 mg, 0.21 mmol), triphenylphosphine (132.1 mg, 0.50 mmol) and 2-bromo-2-phenylacetic acid (54.1 mg, 0.25 mmol) was stirred under reflux for 12 h. The reaction was quenched with water (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried over $MgSO_4$. This organic layer was filtered and concentrated under reduced pressure, and then the crude product was purified by preparative TLC (SiO_2, ethyl acetate/hexane=1:5) to give the desired β-lactam.[8]

Furthermore, it was found that the polymer-supported phosphine could be used instead of triphenylphosphine and that the polystyryl-diphenylphosphine[9] could promote the reaction in good yield with high *trans*-selectivity (Scheme 2). In this case, the by-product, the polystyryl-diphenylphosphine oxide, could be separated by filtration, so that the purification became much easier.



Yield 72 %, *trans* : *cis* = 90 : 10

Scheme 2

In summary, we found that the several β-lactams were smoothly constructed in one step by triphenylphosphine in good yields with high *trans*-selectivity. Moreover, the polystyryl-diphenylphosphine was also found to promote the same reaction effectively. These reactions are very versatile reactions in organic synthesis because the operations are very simple, the starting materials are easily available and β-lactams are obtained with the high *trans*-selectivity. Further examination for clarification of mechanism is now in progress.

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4. The reaction was also carried out under reflux conditions in other solvents, toluene and MeCN. However, the best results were obtained under benzene reflux condition.
5. We investigated the effects of the several substituents on the nitrogen atom of the imine. Then, *p*-methoxyphenyl group was found to be the best substituent to achieve the highest yield and selectivity.
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7. Although there was the possibility that the reaction proceeded *via* the formation of ketenes, the product was obtained with *trans*-selectivity even in the reaction of 2-bromopropionic acid (Entry 7). So, this reaction mechanism was thought as that illustrated in Scheme 1. The *cis*-selective β-lactam formation of alkyl ketenes with imines was reported; C. Palomo, J. M. Ontoria, J. M. Odriozola, J. M. Alzpurua, and I. Ganboa, *J. Chem. Soc., Chem. Commun*., 1990, 248.
8. ^{1}H-NMR (300 MHz, $CDCl_3$): *trans*-isomer; δ 7.25-7.38 (m, 11H), 6.84 (d, 2H, J = 8.7 Hz), 4.88 (d, 1H, J = 1.8 Hz), 4.21 (d, 1H, J = 1.8 Hz), 3.74 (s, 3H). *cis*-isomer; δ 7.33 (d, 2H, J = 9.0 Hz), 6.98-7.12 (m, 9H), 6.83 (d, 2H, J = 9.3 Hz), 5.39 (d, 1H, J = 6.3Hz), 5.00 (d, 1H, J = 6.3 Hz), 3.77 (s, 3H). IR(KBr): 3100-2900, 1740, 1510, 1490, 830, 820.
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