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SELECTIVE SYNTHESIS OF β-AMINO ESTERS AND β-LACTAMS BY RHODIUM-CATALYZED REFORMATSKY-TYPE REACTION

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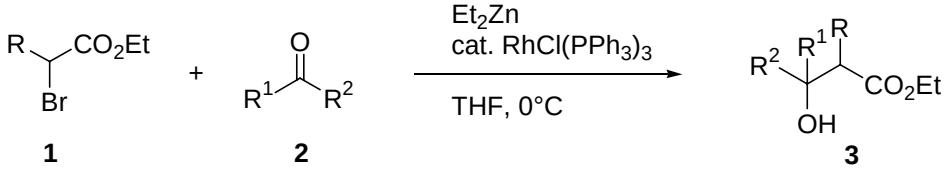
Abstract - β-Amino esters and β-lactams are synthesized selectively from aldimines and ethyl bromoacetate by applying a simply modified rhodium-catalyzed Reformatsky-type reaction.

β-Lactam antibiotics are a large class of clinically important drugs, which have, over the year, provoked an extraordinary amount of activity by synthetic organic chemists.[1] The basic β-lactam skeletons are often synthesized from the corresponding β-amino acids or their esters by intramolecular cyclizations. Meanwhile, β-amino acids hold an important place in pharmacology,[2] since they play not only as precursors of β-lactam antibiotics, but also as constituents of biologically active unnatural peptides.[3] It has also been reported that cyclic β-amino acids exhibit excellent antifungal activities.[4] In the synthesis of β-amino acids or β-amino esters, difficulties were sometimes encountered to produce the desired compound as the sole product, which usually accompanied with a formation of β-lactams. Therefore, development of a novel and simple methodology for the selective preparation of β-amino acids and β-lactams would be highly desirable in organic synthesis. Although numerous methods for constructing a β-lactam framework have been described,[5] relatively little attention has been focused on the selective formation of β-amino esters.[6] A straightforward manner for obtaining β-amino esters is considered to be

the addition of the Reformatsky reagents[7] to aldimines; however, non-selective formation of β-amino esters and β-lactams in ratios depending on the conditions employed often is observed.[6] Recently, Adrian and his co-workers reported the selective formation of β-amino esters by applying the Refromatsky reaction, where they observed that the *ortho*-methoxyphenyl substituent on the imine nitrogen played a crucial role.[8] We have also disclosed a novel rhodium-catalyzed Reformatsky-type reaction recently in which β-hydroxy esters (**3**) are produced from the carbonyl compounds (**2**) and α-bromo esters (**1**) under mild reaction conditions.[9] (Scheme 1)

Scheme 1



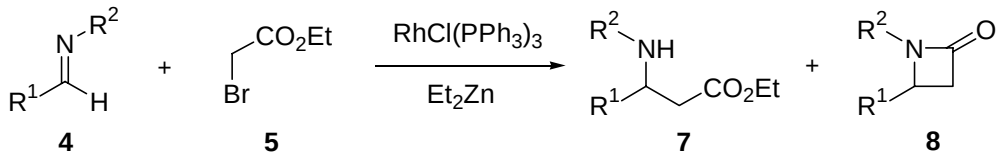
In order to extend the usefulness of this newly developed reaction in organic synthesis, we already applied this methodology to the synthesis of optically active β-amino esters, successfully.[10] Here, we would like to report our further application of this methodology to the synthesis of β-amino esters (**7**) and β-lactams (**8**), selectively, from aldimines (**4**) and ethyl bromoacetate (**5**) by simply controlling the reaction conditions.

We first screened a variety of reaction conditions, such as solvents, reaction temperature, the amounts of Wilkinson's catalyst and diethylzinc, additives, and so on. After some exploration, we could finally find optimal reaction conditions for obtaining β-amino esters and β-lactams, selectively.[11] The results are summarized in Table 1.

When the reactions were carried out in THF at 0°C in the presence of $RhCl(PPh_3)_3$ (5 mol%) and diethylzinc (4 mol equivalents), β-amino esters were produced exclusively in moderate to good yields without giving β-lactams regardless of the substituents on the aldimine nitrogens. On the other hand, β-lactams were selectively formed in toluene at 40°C. Based on these results, it was figured out that the substituents on the aromatic rings having *meta*- and *para*-methoxy groups at the imine nitrogens, and also

substitution patterns on R^1 do not seem to affect the selectivity. (Entries 6 and 7) In Entries 8 and 9, unsatisfactory results were obtained due to the instability of those substrates under the reaction conditions.

Table 1.



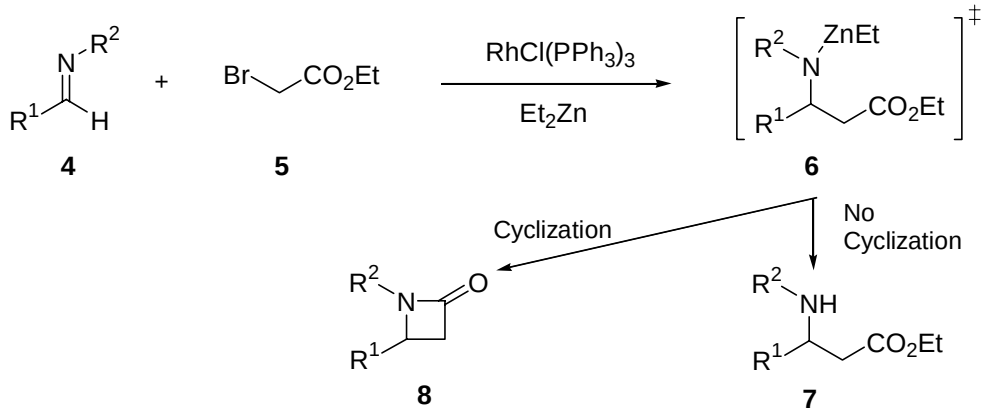
4 **5** **7** **8**

Entry	R^1	R^2	Yield (%) THF, 0°C **7**	**8**	PhMe, 40°C **7**	**8**
1	Ph	Ph	70	–	–	65
2	2-$MeOC_6H_4$	Ph	61	–	–	49
3	3-$MeOC_6H_4$	Ph	62	–	–	63
4	4-$MeOC_6H_4$	Ph	64	–	–	67
5	2,4-$(MeO)_2C_6H_3$	Ph	70	–	–	50
6	Ph	3-$MeOC_6H_4$	65	–	–	62
7	Ph	4-$MeOC_6H_4$	46	5	–	55
8	3-$MeOC_6H_4$	$CH_2C_6H_5$	28	–	–	42
9	cinnamyl	Ph	43	–	–	–
10	Ph	2-$MeOC_6H_4$	69	–	56	–
11	Ph	2,4-$(MeO)_2C_6H_3$	71	–	49	–
12	2,4-$(MeO)_2C_6H_3$	2,4-$(MeO)_2C_6H_3$	77	–	53	–

However, in the case of aldimines possessing *ortho*-methoxyphenyl group on the imine nitrogens, only β-amino esters were produced exclusively even in toluene at 40°C without giving β-lactams (Entries 10, 11, and 12). The observations obtained here are in good accordance with the results reported by Adrian and his co-workers, and this fact would suggest that the reactions also proceeded through similar zinc amide intermediates (**6**)[12] under the rhodium-catalyzed reaction conditions for the conventional

Reformatsky reaction as depicted in Scheme 2.

Scheme 2



Thus, we have succeeded in the preparation of β-amino esters and β-lactams, selectively, by simply changing the solvent and reaction temperature in the rhodium-catalyzed Reformatsky-type reaction. Further applications of this methodology to the synthesis of biologically active compounds including natural products are in progress in this laboratory.

ACKNOWLEDGMENT

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11. **General procedure for selective formations of β-amino esters (7) and β-lactams (8):** To a stirred solution of $RhCl(PPh_3)_3$ (5 mol %) in THF (5 mL)(Condition A for obtaining β-amino esters) or in toluene (5 mL)(Condition B for obtaining β-lactams) at 0°C were added ethyl bromoacetate (**5**) (1.1 mmol), imine (**4**) (1 mmol), and a *ca*. 1.0 M hexane solution of Et_2Zn (4 mmol). After stirring for 30 min at 0°C (Condition A) or at 40°C (Condition B), saturated aqueous $NaHCO_3$ was added. The reaction mixture was filtered, and the filtrate was partitioned between EtOAc and brine. The organic extract was dried (Na_2SO_4), and the residue was purified by column chromatography on silica gel.
12. Adrian *et al*.[8] reported that their reactions proceeded both in CH_2Cl_2 and THF to give the desired compounds selectively in reasonable yields. However, reaction times in THF were typically four to ten times longer. On the other hand, in our experiments the observed selectivity for obtaining β-amino esters and β-lactams in CH_2Cl_2 was diminished compared to the cases in THF and toluene.