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The simple and selective synthesis of 3-amino-2,2-difluorocarboxylic esters and difluoro-β-lactams using ethyl bromodifluoroacetate in the presence of rhodium catalyst

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Abstract—Treatment of imines (**5**) with ethyl bromodifluoroacetate (**1**) and Et_2Zn in the presence of $RhCl(PPh_3)_3$ in anhydrous medium gave difluoro-β-lactams (**7**) in good to excellent yields, while 3-amino-2,2-difluorocarboxylic esters (**6**) were obtained in good yields by adding $MgSO_4{\cdot}7H_2O$ to the reaction medium.

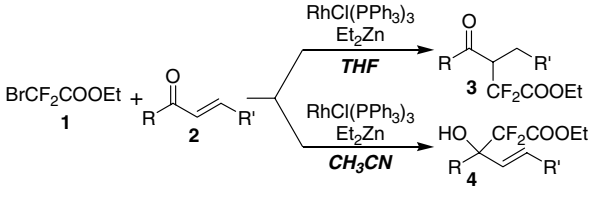
The β-lactam antibiotics including penicillins and cephalosporins have been used widely in the clinical field. Their biological activity is recognized as inhibition of the enzyme synthesizing bacteria's cell walls.[1] β-Lactam ring is known as an important component to exhibit the antibiotic effect. Furthermore, β-lactams are one of the most important synthetic intermediate for the β-amino acid derivatives. Although both β-lactam and β-amino acid derivatives can be easily synthesized using Reformatsky-type reaction[2] or aldol-type reaction[3] of imines, the selective synthesis of these compounds is difficult.

On the other hand, rhodium mediated organic reaction is one of the most useful carbon–carbon bond formation procedures. This can be used for carbonylation, hydrogenation, and methathesis.[4] The rhodium-catalyzed 1,4-addition reaction of organoboronic acids, organostannanes, or organosilanes to α,β-unsaturated carbonyl compounds has also been reported.[5]

Recently, we reported the novel trifluoromethylation at the α-position of α,β-unsaturated ketones using CF_3I, Et_2Zn, and $RhCl(PPh_3)_3$.[6] Furthermore, we reported that ethyl bromodifluoroacetate (**1**) reacted with α,β-unsaturated ketones (**2**) in the presence of Et_2Zn and $RhCl(PPh_3)_3$ to give the novel products (**3**), where the CF_2COOEt group was introduced to the α-position of α,β-unsaturated ketones, or the Reformatsky-type 1,2-addition product (**4**) in good yields selectively by choosing the solvents (Scheme 1).[7]

In order to extend our previous results, we attempted to examine the reaction of imines with **1** and Et_2Zn in the presence of $RhCl(PPh_3)_3$. Honda et al. reported that the reaction of $BrCH_2COOEt$ and imines (**5**) with Et_2Zn in the presence of $RhCl(PPh_3)_3$ gave the β-lactams and 3-aminocarboxylic esters depending on the solvents and temperature.[8] Generally, the Reformatsky reaction using halodifluoroacetate and imines with Zn powder gave the difluoro-β-lactams (**7**).[9] So we expected that **6** and **7** could be synthesized selectively by the examination of reaction conditions.

Herein, we would like to report a simple and selective synthesis of 3-amino-2,2-difluorocarboxylic esters (**6**) and difluoro-β-lactams (**7**) (Scheme 2).



Scheme 1. Reaction of **1** with **2** in the presence of $RhCl(PPh_3)_3$.

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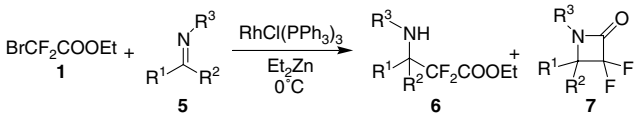


Scheme 2. Reaction of **1** with **5** in the presence of $RhCl(PPh_3)_3$.

The effect of solvents and amounts of Rh catalyst, **1** and Et_2Zn are summarized in Table 1. Based on our previous result,[7] we examined the reaction of **1** and *N*-benzylideneaniline (**5a**) in CH_3CN, but neither **6** nor **7** was hardly obtained. Using THF as the solvent, **7** was obtained in a good yield, although **6** was hardly obtained as shown in entry 2. A long reaction time was needed in the absence of Rh catalyst (entry 1). From the examination of several conditions, we found that entry 6 is the best condition to obtain the difluoro-β-lactams (**7**).

Based on the above result, we applied the reaction to other various imines (Table 2). As shown in entries 1–9, the aromatic aldimines (**5a–f**) gave the corresponding difluoro-β-lactams (**7**) in good to excellent yield, although the *p*-nitrophenyl and the aliphatic aldimines (**5g–i**) gave poor results. The substituents on the nitrogen atom hardly affected the reaction as shown in entries 1, 2, 10, and 11. The difluoro-β-lactams (**7**) were also obtained in poor to moderate yields using ketimines (**5l**,**m**) as shown in entries 12 and 13.

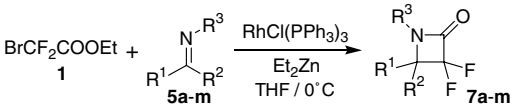
It is interesting to note that Honda and colleague obtained the β-lactams and amino esters by changing the solvent.[8] On the other hand, we only obtained the corresponding difluoro-β-lactams (**7**), even if a variety of solvents were examined. We thought that the fluorine group might play an important role to form **7**. However, recently, Fujii and co-workers reported the reaction of **1** with an imine (**5**) to give 3-amino-2,2-difluorocarboxylic ester (**6**) in a moderate yield on the way to the peptide isostere.[10] We were interested in their results, since, we obtained **7** but not **6** in most cases. Therefore, we read their experimental part carefully, and found they formed the imine in the presence of molecular sieves and used them without isolation. We assumed that H_2O on the molecular sieves was essential for the formation of **6**, though they did not mention this fact. To confirm our assumption, we examined the reaction of **5b** in the presence or absence of traces of H_2O. The results are shown in Table 3.

As shown in Table 3, when pure **5b** was used in this reaction, **7b** was the primary product (entry 1). Now, we paid attention to the fact that Fujii's group used the imine without isolation. We used $MgSO_4$ in the place of molecular sieves. Thus, we formed **5b** from benzaldehyde and benzylamine in the presence of $MgSO_4$ in situ, followed by the reaction with **1** in the presence of Et_2Zn and $RhCl(PPh_3)_3$, and obtained **6b** as a major product

Table 1. Examination of the reaction conditions

Entry	$RhCl(PPh_3)_3$ (mol %)	Solvent	Temperature (°C)	**1** and Et_2Zn (equiv)	Time (h)	Yield of **7** (%)
1	None	THF	0	3.0	7	60
2	1	THF	0	3.0	3	62
3	5	THF	0	3.0	3	48
4	10	THF	0	3.0	1	22
5	1	Et_2O	0	3.0	2	48
6	1	CH_2Cl_2	0	3.0	2	67
7	1	DMF	0	3.0	22	Trace
8	1	Toluene	0	3.0	23	49

Table 2. Reaction of **1** with various imines



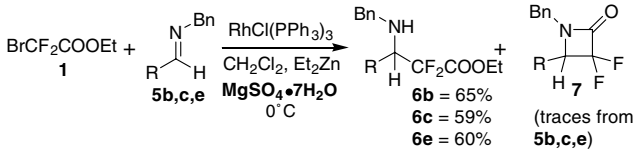
Entry	Compound **5**				Time (h)	Yield of **7** (%)
	R^1	R^2	R^3			
1	Ph	H	Ph	**a**	2	67
2	Ph	H	Bn	**b**	1	83
3	4-MeO–Ph	H	Bn	**c**	6	93
4	4-^{i}Pr–Ph	H	Bn	**d**	1	80
5	4-Cl–Ph	H	Bn	**e**	1	82
6	4-MeOOC–Ph	H	Bn	**f**	1	80
7	4-NO_2–Ph	H	Bn	**g**	7	Trace
8	C_6H_{11}	H	Bn	**h**	18	35
9	^{t}Bu	H	Bn	**i**	17	NR
10	Ph	H	Me	**j**	2	62
11	Ph	H	^{t}Bu	**k**	21	86
12	Ph	Me	Bn	**l**	2	44
13	Ph	Ph	Bn	**m**	46	8[a]

[a] The reaction was refluxed.

Table 3. Examination of the selective synthesis of **6** and **7**

Entry	**5b**	Additive (equiv)	Time (h)	Yield of **6b** (%)	Yield of **7b** (%)
1[a]	Isolated	None	1	Trace	83
2	Synthesized by $MgSO_4$	None	3	46	8
3	Synthesized and then removed of $MgSO_4$	None	1	4	59
4	Isolated	$MgSO_4$ (2)	1	5	64
5	Isolated	$BnNH_2$ (0.1)	1	3	80
6	Isolated	H_2O (1)	2	48	16
7	Isolated	$MgSO_4{\cdot}7H_2O$ (1)	1	65	Trace

[a] The entry 1 of Table 3 is the same result with the entry 2 of Table 2.



Scheme 3. Reaction of **1** with **5** in the presence of $RhCl(PPh_3)_3$ and $MgSO_4{\cdot}7H_2O$.

(entry 2). These results supported our assumption that H_2O played an important role for the selective formation of **6** and **7**. By the examination of several reaction conditions, the addition of equimolar amount of $MgSO_4{\cdot}7H_2O$ was found to lead to the best formation of **6**. The application to other substrates (**5c**,**e**) also gave the similar results in moderate to good yields (Scheme 3).

In conclusion, we could obtain difluoro-β-lactams (**7**) in good to excellent yields using rhodium-catalyzed Reformatsky-type reaction. Moreover, we could obtain 3-amino-2,2-difluorocarboxylic esters (**6**) in good yields by adding $MgSO_4{\cdot}7H_2O$ to the reaction medium. This is the first report for the selective synthesis of **6** and **7** without the troublesome handling. In addition, compounds **6** and **7** are fluorine analogs of β-amino acid derivatives and are very important compounds in pharmacology. We provided a new procedure to synthesize each by adding $MgSO_4{\cdot}7H_2O$ or not. There are no reports up to now that difluoro-β-lactams and 3-amino-2,2-difluorocarboxylic esters were selectively synthesized only from the addition of an additive. We believe that this reaction could be widely used in various fields.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.09.031.

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