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The synthesis of β-lactams via a one-pot Reformatsky reaction of imines promoted by Zn/Cp_2TiCl_2 (cat.)

Lei Chen, Gang Zhao* and Yu Ding*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling lu, Shanghai 200032, PR China

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Abstract—In the presence of Zn/Cp_2TiCl_2 (cat.) α-bromoacetates, γ-bromocrotonates or α-bromomethylacrylates react with imines in one-pot to form β-lactams, 3-vinyl-β-lactams or α-methylene-γ-lactams, respectively, at room temperature without the need for pretreatment of the solvent and Zn.

Since Gilman[1] and Speeter reported the Reformatsky addition reaction to imines in 1943 it has been employed as a method to synthesize β-lactams, β-amino acids and their derivatives.[2] β-Lactams are very important compounds existing widely in various antibiotics and other natural products.[3] However, the classical Reformatsky reaction usually takes a long time under reflux and the selectivity is not good. Papers on the modification of the classical Reformatsky reaction[4,5] and new Reformatsky-type reactions have been published.[6] We have reported that bromoacetate and its vinylogous derivatives can add rapidly to carbonyl groups and electron-deficient alkenes such as 1,1-dicyano or 1-cyano-1-sulfonyl alkenes at room temperature under Zn/Cp_2TiCl_2 (cat.) promotion in one-pot.[7] These results encouraged us to extend this system to imines. Indeed, in the presence of Zn/Cp_2TiCl_2 (cat.) imines react smoothly with α-bromoacetates, γ-bromocrotonates or α-bromomethylacrylates in one-pot to form β-lactams, 3-vinyl-β-lactams or α-methylene-γ-lactams, respectively, with varying selectivity. Herein we would like to report our results.

The reaction proceeded in THF at room temperature, and was finished within 5–10 minutes and gave good yields. The results in Table 1 show that aromatic aldimines react with α-bromoacetates to produce β-lactams **3** with the *cis* isomer being the major product in satisfactory to good yields. The stereoselectivity is related to the bulkiness of the α-substituent in the α-bromoacetates (entries 4 and 11). The β-amino acid **4** with the *syn* configuration was always formed as a by-product in various ratios (apart from entries 9 and 10); it was the only product in the case of *N*-α-naphthylbenzylidenimine (entry 5). This may be due to the larger steric hindrance of the *N*-α-naphthyl group, which hinders the cyclization of the intermediate. Enolizable aliphatic aldimines also reacted smoothly with ethyl α-bromopropionate (entries 9 and 10) in good yield, but no β-amino acid was formed. α,β-Unsaturated aldimines also reacted (entries 8, 12, 14) to give **3**. Isomerizable *N*-butylimine, *N*-benzylimine and *N*-tosylimine did not react.

This reaction was extended successfully to γ-bromocrotonates, a vinylogous derivative of α-bromoacetates (Table 2), as there are only a few papers on the Reformatsky reactions of γ-bromocrotonates with imines in the literature.[8] The results listed in Table 2 show that the reaction product of γ-bromocrotonates with imines depends on the R^1 group. When R^1 is an aromatic group (entries 1–6), only *trans* 3-vinyl-β-lactams **6** were obtained, from α-attack of the γ-bromocrotonate to the imine, but when R^1 is an aliphatic alkyl (*iso*-Pro, *cyclo*-Hex) (entries 9 and 10) or an alkenyl group (*trans*-styryl) (entries 7 and 8), only the δ-amino acid **7** was obtained in good yield from γ-attack of the γ-bromocrotonate to the imine. In the latter case no 1,4-addition occurred. Isomerizable *N*-butylimines and *N*-benzylimine also did not react, similar to α-bromoacetates. It is interesting that *trans*-3-vinyl-β-lactams or δ-amino acids could be obtained selectively from imines of different structure, hence this method will be useful for their preparation.

Keywords: imines; azetidinones; biscyclopentadienyltitanium dichloride; Reformatsky reaction.

* Corresponding authors. Tel: 86-021-64163300; fax: 86-021-64166128; e-mail: dingyu@pub.sioc.ac.cn

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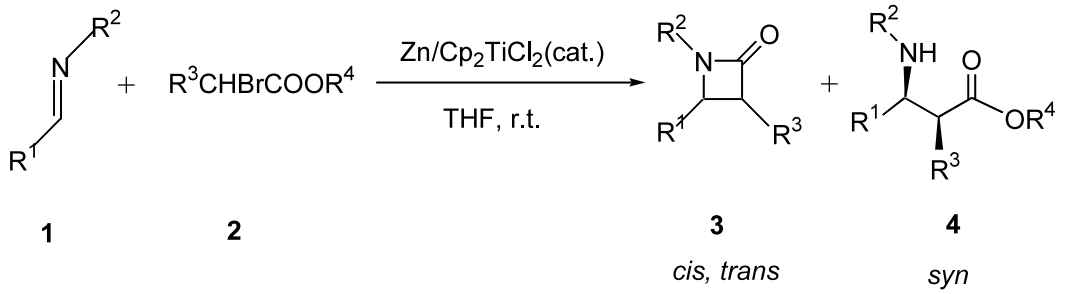
Table 1. The Reformatsky reaction of imines and α-bromoalkanoates[a]

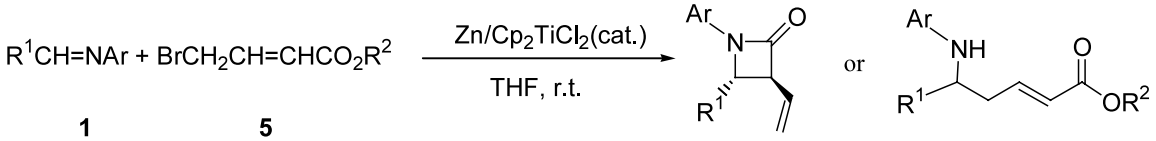


1 **2** **3** *cis, trans* **4** *syn*

Entry	R^1	R^2	R^3	R^4	Time (min)	Yield% (**3**/**4**)[b]	*cis*:*trans*[c] (**3**)
1	Ph	Ph	H	Et	6	52/38	–
2	Ph	Ph	Me	Et	5	80/12	91:9
3	Ph	4-$MeOC_6H_4$	H	Et	6	50/30	–
4	Ph	4-$MeOC_6H_4$	Me	Et	8	77/7.5	85:15
5	Ph	α-Naphthyl	Me	Et	7	nd[d]/55	–
6	*p*-FC_6H_4	4-$MeOC_6H_4$	Me	Et	5	81/10	92:8
7	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	Et	9	78/14	95:5
8	*trans*-Styryl	4-$MeOC_6H_4$	Me	Et	10	75/13	72:28
9	Isopropyl	4-$MeOC_6H_4$	Me	Et	8	67/nd	87:13
10	Cyclohexyl	Ph	Me	Et	7	66/nd	83:17
11	Ph	4-$MeOC_6H_4$	Et	Me	6	75/13	97:3
12	*trans*-Styryl	4-$MeOC_6H_4$	Et	Me	5	81/15	82:18
13	*p*-FC_6H_4	4-$MeOC_6H_4$	Me	Et	60[e]	60/7	85:15
14	*trans*-Styryl	4-$MeOC_6H_4$	Et	Me	70[e]	65/12	73:27

[a] The ratio of Schiff's base, α-bromoalkanoate, Cp_2TiCl_2 and Zn powder: 1:1.5:0.1:1.2 in 2 mmol scale.
[b] Isolated yield based on Schiff's bases.
[c] Isomer ratios were determined by ^1H NMR (300 MHz).
[d] Not detected.
[e] Refluxed in THF without Cp_2TiCl_2.

Table 2. Reformatsky reaction of arylaldimines and 4-bromocrotonates[a]



1 **5** **6** *trans* **7**

Entry	R^1	Ar	R^2	Time (min)	Product	Yield%[b]
1	Ph	Ph	Me	10	**6**	80
2	Ph	Ph	Et	9	**6**	78
3	Ph	4-$MeOC_6H_4$	Me	6	**6**	81
4	Ph	4-$MeOC_6H_4$	Et	8	**6**	80
5	*p*-FC_6H_4	4-$MeOC_6H_4$	Me	7	**6**	82
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	10	**6**	77
7	*trans*-Styryl	Ph	Me	10	**7**	65
8	*trans*-Styryl	4-$MeOC_6H_4$	Me	10	**7**	67
9	Isopropyl	4-$MeOC_6H_4$	Me	8	**7**	63
10	Cyclohexyl	Ph	Me	9	**7**	70

[a] The ratio of Schiff's base, α-bromoalkanoate, Cp_2TiCl_2 and Zn powder: 1:1.5:0.1:1.2 in 2 mmol scale.
[b] Isolated yield based on Schiff's bases.

By using our system α-methylene-γ-lactams have been conveniently prepared in one-pot from α-bromomethyl acrylate and various *N*-aryl imines in good yield.

As mentioned above and in our previous work,[7] Cp_2TiCl_2 is a very efficient mediator for promoting the Reformatsky addition to aldehydes, ketones, imines

and electron-deficient olefins. We have suggested a mechanism[7b] for the one-pot Reformatsky reaction: Cp_2TiCl_2 promotes the formation of Reformatsky reagents through activating the Zn powder, but it is still necessary to clarify the role that Cp_2TiCl_2 plays in the activating process. Three experiments were carried out: (1) Imine (**1**, Table 1, $R^1=R^2=Ph$) and α-bromopropionate were added to a solution of $[Cp_2TiCl]_2$, prepared from zinc powder and Cp_2TiCl_2 according to the literature,[9] the green solution quickly turned to red but the expected reaction did not occur. This means that the three valent titanium species $[Cp_2TiCl]_2$ itself could not promote the addition of α-bromopropionate to the imine in the absence of zinc. (2) At room temperature zinc powder (1.2 molar ratio to imine) was added to a mixture of α-bromopropionate (1.5 molar ratio to imine) and Cp_2TiCl_2 (0.1 molar ratio to imine) in THF, the solution turned to green, the zinc disappeared quickly and a brown solution formed. Then the imine (**1**, Table 1, $R^1=p$-FC_6H_4, $R^2=4$-$MeOC_6H_4$) was added and the mixture stirred for a while. After the usual work-up the β-lactam (*cis*:*trans*=85:15) was isolated in a 50% yield, which is close to the result of the one-pot reaction. (3) In contrast with the negative result in the first experiment, when a pre-prepared green solution of $[Cp_2TiCl]_2$ was added to the Reformatsky reaction mixture consisting of imine (**1**, Table 1, $R^1=$ *trans*-styryl, $R^2=4$-$MeOC_6H_4$): α-bromopropionate: zinc powder (molar ratio=1:1.5:1.2) in THF at room temperature, the expected Reformatsky addition reaction occurred, the β-lactam (60% yield, *cis*:*trans*=70:30) and β-amino acid (10% yield, *syn*:*anti*>99:1) were obtained. This result is almost the same as that of the one-pot reaction (Table 1, entry 8).

Based on the above facts we think that a SET mechanism may be involved in the activation process of the Zn powder by Cp_2TiCl_2 to promote the formation of the Reformatsky reagent.

It is well known that Cp_2TiCl_2 is easily reduced by Zn to Ti(III), which is a better single electron transfer reagent than Zn[10] itself and, therefore, can donate one electron to α-bromoacetate to form the alkoxycarbonylmethyl radical and bromide anion at room temperature. The radical reacts with Zn (or Zn^+) to form ZnCHRCOOR′ (or $^+$ZnCHRCOOR′) and then BrZnCHRCOOR′ at room temperature. The Reformatsky reagent formed in situ is active enough to add to the imine.

In conclusion, Zn/Cp_2TiCl_2 (cat.) is a good mediator system for promoting the formation of the Reformatsky reagent, subsequent addition to an imine in one-pot forms a β-lactam or a γ-lactam in good yield and diastereoselectivity. Compared to the classical Reformatsky reaction our modification is much easier due to there being no need for activation of the zinc in advance, no strict anhydrous pretreatment of the solvent and also due to the very fast reaction rate at room temperature.

Typical procedure: To a stirred solution of imine **1** (2 mmol), Cp_2TiCl_2 (0.05 g, 0.2 mmol) in THF (8 ml) were added α-bromoacetate (or 4-bromocrotonate, α-bromomethylacrylate) (3 mmol) and Zn powder (2.4 mmol) at room temperature. The solution turned to green quickly and the Zn powder began to disappear. After Zn was consumed almost completely, the reaction mixture was stirred continuously for 5 min or more and then 5% Na_2CO_3 aqueous solution (10 ml) was added to quench the reaction. The mixture was extracted with ether (4×10 ml). The organic layers were combined and washed with saturated brine, then dried over Na_2SO_4. After removal of the solvent the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether/ethyl acetate) to give the product.[11]

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11. Data of representative products: 1-(*p*-Methoxyphenyl)-4-(4′-fluorophenyl)-3-methyl-2-azetidinone. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, 3H, *cis*, $J=7.5$ Hz), 1.48 (d, 3H, *trans*, $J=7.5$ Hz), 3.08 (dq, 1H, *trans*, $J=2.4$, 7.5 Hz), 3.66 (dq, 1H, *cis*, $J=5.8$, 7.5 Hz), 3.77 (s, 3H), 5.15 (d,

1H, $J=5.8$ Hz), 6.77–7.30 (m, 8H); EIMS m/z (%) 285 (M^+, 27.32), 149 (100); IR (KBr) 1733, 1519, 1255, 1226 cm^{-1}. Anal. calcd for $C_{17}H_{16}FNO_2$: C, 71.56; N, 4.91; H, 5.65. Found: C, 71.68; N, 4.78; H, 5.59. Ethyl 3-(*p*-fluorophenyl)-3-(4′-methoxyanilino)-2-methyl-propanoate. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, 3H, $J=7.2$ Hz), 1.15 (d, 3H, $J=7.6$ Hz), 2.89 (dq, 1H, $J=5.6$, 7.6 Hz), 3.68 (s, 3H), 4.06 (q, 2H, $J=7.2$ Hz), 4.60 (d, 1H, $J=5.6$ Hz), 6.45–7.31 (m, 8H); EIMS m/z (%) 331 (M+, 9.46), 230 (100); IR (film) 3379, 1722, 1518, 1200 cm^{-1}; HRMS calcd for $C_{19}H_{22}FNO_3$: 331.1584. Found: 331.1589. 1-(4′-Methoxyphenyl)-3-vinyl-4-(*p*-fluorophenyl)-2-azetidinone. ^1H NMR (300 MHz, $CDCl_3$): δ 3.70–3.74 (m, 1H), 3.75 (s, 3H), 4.77 (d, 1H, $J=2.3$ Hz), 5.32–5.40 (m, 2H), 5.99–6.01 (m, 1H), 6.78–7.35 (m, 8H); m/z (%) 297 (M^+, 15.97), 148 (100); IR (film): 1739, 1517, 1389, 1247, 823 cm^{-1}. HRMS calcd for $C_{18}H_{16}FNO_2$: 297.1165. Found 297.1136. Methyl 7-phenyl-5-(4′-methoxyanilino)-2,6-heptadienoate. ^1H NMR (300 MHz, $CDCl_3$): δ 2.57–2.62 (m, 2H), 3.71 (s, 6H), 4.06–4.12 (m, 1H), 5.94 (d, 1H, $J=15.5$ Hz), 6.15 (dd, 1H, $J=6.0$, 15.9 Hz), 6.56–6.77 (m, 5H), 6.94–7.36 (m, 6H); EIMS m/z (%) 337 (M^+, 2.28), 238 (100); IR (film): 3384, 2834, 1721, 1513, 1242, 821 cm^{-1}. HRMS calcd for $C_{21}H_{23}NO_3$: 337.1678. Found 337.1674.