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Tetrahedron Letters 47 (2006) 1973–1975
Tetrahedron Letters

Reductive Mannich-type reaction using the composite reagents of phosphine and Lewis acid

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Received 21 December 2005; revised 11 January 2006; accepted 13 January 2006

Abstract—We found that the combination of Ph_3P and $TiCl_4$ was the excellent promoter for reductive Mannich-type reaction of *S*-2,4,6-triisopropylphenyl 2-bromopropanethioate with several imines and that the corresponding products were obtained in good yields with high *anti*-selectivity.

Mannich-type reaction is one of the most versatile and important reactions for the carbon–carbon bond formation in organic syntheses and the products, β-amino-carbonyl compounds, are useful precursors for various biological active compounds, such as β-amino acids and β-lactams, etc. So, until now, numerous useful methods were developed.[1] For example, the (L)-proline was known to be the excellent promoter for Mannich reaction in high yields with good *syn*-selectivity[1d,e] and the reaction of the silyl enol ether derivatives with imines was reported as one of the other useful methods.[2] However, there are few reports that Mannich reaction proceeded with high *anti*-selectivity. So it was necessary to develop the new methodology for *anti*-selective Mannich reaction.

On the other hand, in recent years, we have been studying the composite reagents, the combinations of phosphine and Lewis acid,[3,4] which showed the interesting and characteristic reducing ability. It has been already reported that the Reformatsky-type reaction of α-bromocarbonyl compounds was promoted by this combination to give the desired adducts in good yields with high diastereoselectivity[3b,3c] and that the reductive Claisen-type condensation of various α-bromothioesters proceeded in good yields under mild conditions (Scheme 1).[3d]

As shown in Scheme 1, when the imines were examined as the electrophiles in place of aldehydes or thioesters, Mannich-type reaction proceeded. In this letter, we would like to describe the first example of reductive Mannich-type reaction mediated by the combination of phosphine and Lewis acid in good yields with high *anti*-selectivity.

First, we carried out the reaction of *S*-mesityl 2-bromopropanethioate and imine, which was derived from *p*-chlorobenzaldehyde and *p*-anisidine, using the combination of Ph_3P and $TiCl_4$ in CH_2Cl_2. Then, it was found that the Mannich-type reaction proceeded and the β-aminothioester derivative was obtained. So, we optimized several reaction conditions and found that the Mannich-type reaction was most effectively promoted by the combination of Ph_3P and $TiCl_4$ in CH_3CN.

Next, we investigated the effects of the substituents on sulfur atoms of thioesters (**1a**–**e**) in the reaction with imine (**2**) under the optimized conditions. The results are summarized in Table 1.

As can be seen from Table 1, when the bulkier substituents were used, the diastereoselectivities of products became higher. Among those thioesters examined, it was found that the thioester derived from the 2,4,6-triisopropylbenzenthiol (**1e**) was the most effective substrate to achieve the highest diastereoselectivity (entry 5).

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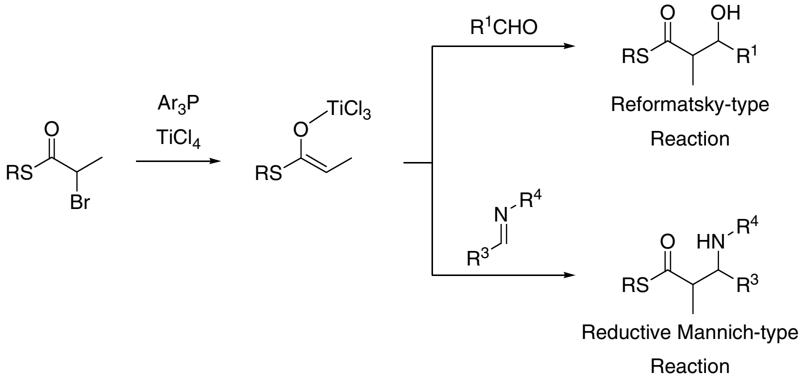
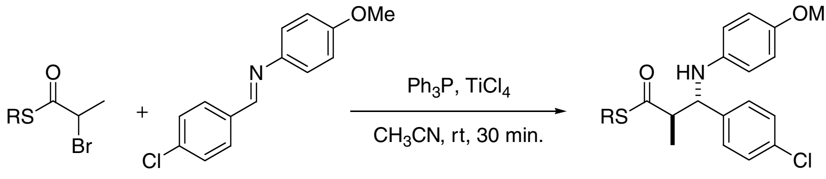
doi:10.1016/j.tetlet.2006.01.106



Scheme 1.

Table 1. The effects of the substituents on sulfur atom of α-bromothioesters[a]



1 **2a** **3**

Entry	Substrate **1** (*RS*)		Product	Yield[b] (%)	*anti*:*syn*
1	**1a**	EtS	**3aa**	89	69:31[c]
2	**1b**	^{t}Bu	**3ba**	89	92:8[d]
3	**1c**	PhS	**3ca**	89	81:19[d]
4	**1d**	2,4,6-$Me_3C_6H_2S$	**3da**	97	95:5[d]
5	**1e**	2,4,6-^{i}$Pr_3C_6H_2S$	**3ea**	95	97:3

[a] **1**/**2a**/Ph_3P/$TiCl_4$ = 1.5:1.0:1.5:1.5.

[b] Isolated yield.

[c] Determined by ^{1}H MNR.

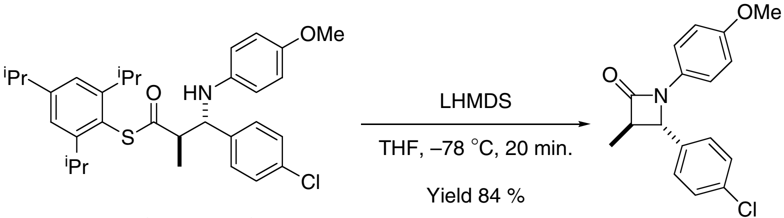
[d] Determined by HPLC.

The relative stereochemistry of the product (**3ea**) was assigned by the following means: the major product, which could be purified by recrystallization, was converted into the corresponding β-lactam (**4**) without racemization, using LHMDS in THF at −78 °C (Scheme 2).[5] And the vicinal coupling constants of C3 and C4 protons ($J = 2.1$ Hz) were compared with those of similar compounds in the literature.[6]

Under the optimized conditions, we carried out the reaction between this bulky thioester, *S*-2,4,6-triisopropylphenyl 2-bromopropanethioate (**1e**), and several imines derived from *p*-anisidine. The results are summarized in Table 2.[7]

As shown in Table 2, although the reaction of the imine derived from pivalaldehyde did not proceed (entry 7), the reactions of other imines, which were derived from the aromatic aldehydes, were achieved in good yields (entries 1–6). Moreover, it was noteworthy that the corresponding β-aminothioester derivatives were obtained with high *anti*-selectivity in any type of imines that had the electron-donating group (entries 1–3) or the electron-withdrawing group (entry 4) in *para*-position of aldehyde moiety.

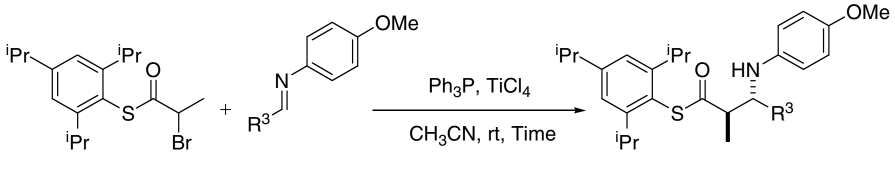
In conclusion, it was found that reductive Mannich-type reaction was promoted by the combination of Ph_3P and $TiCl_4$ in CH_3CN in good yields with high *anti*-selectiv-



3ea (*anti* isomer) **4**

Scheme 2.

Table 2. The reaction of several imines under the optimized conditions[a]



1e **2** **3**

Entry	Substrate **2** (R^3)		Time	Product	Yield[b] (%)	*anti*:*syn*[c]
1	**2a**	p-ClC_6H_4	30 min	**3ea**	95	97:3
2	**2b**	m-ClC_6H_4	1 h	**3eb**	94	96:4
3	**2c**	p-$NO_2C_6H_4$	30 min	**3ec**	99	97:3
4	**2d**	Ph	30 min	**3ed**	100	96:4
5	**2e**	p-$MeOC_6H_4$	3 h	**3ee**	60	95:5
6	**2f**	2-Thienyl	30 min	**3ef**	65	96:4
7	**2g**	^{t}Bu	15 min	**3eg**	0	—

[a] **1e**/**2**/$Ph_3P/TiCl_4$ = 1.5:1.0:1.5:1.5.

[b] Isolated yield.

[c] Determined by HPLC.

ity. This reductive Mannich-type reaction was found to be the very useful reaction in organic synthesis because the operation was very easy, the reaction could be carried out under the mild conditions and the products were obtained with high *anti*-selectivity. Further examination of the asymmetric reaction is now in progress.

References and notes

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7. General procedure for reductive Mannich-type reaction: Under argon atmosphere, to a solution of imine (0.20 mmol) in CH_3CN (3 mL) was added $TiCl_4$ as a hexane solution (3 mol/L, 0.30 mmol) at room temperature. After stirring for 10 min, a solution of α-bromothioester (0.30 mmol) in CH_3CN (2 mL) was added and stirred for additional 10 min. At last, to the reactant, a solution of Ph_3P in CH_3CN (3 mL) was added and stirred for the appropriate reaction time at room temperature. The reaction was quenched with satd $NaHCO_3$ aq (10 mL) and the 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 evaporated under reduced pressure, and then the crude product was purified by preparative TLC (SiO_2, hexane/AcOEt = 5:1) to give the desired β-aminothioesters.