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# Intramolecular Carbotitanation Reaction of Active Methine Compounds Having an Unactivated Alkyne Mediated by $TiCl_4$-$Et_3N$

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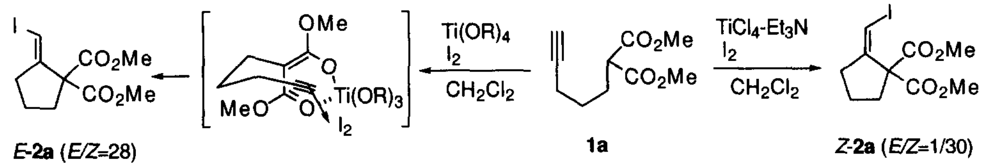
***Abstract***: In the presence of $TiCl_4$ and $Et_3N$, intramolecular carbotitanation reaction of active methine compounds having an unactivated 4-alkynyl group proceeds in a highly *cis*-selective manner to give methylenecyclopentane derivatives in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

***Keywords***: cyclization; titanium and compounds; cyclopentanes; alkynes

In contrast to studies on the carbometalation of unstabilized carbanions having unactivated alkenes and alkynes,[1] there has been a limited number of reports on the intramolecular carbometalation of stabilized carbanions such as metal enolates of active methylene compounds.[2-4] The difficulty of this reaction may be due to the endothermic process involving the conversion of a stabilized enolate anion to an unstabilized $sp^3$ or $sp^2$ carbanion.[5] In this paper, we describe the result of the intramolecular carbotitanation reaction of active methine compounds having an unactivated 4-alkynyl group which proceeds in a highly *cis*-selective manner in the presence of $TiCl_4$ and $Et_3N$.

We recently reported that the iodocarbocyclization reaction of malonate derivatives having unactivated alkenes and alkynes proceeds in a highly stereospecific manner in the presence of $I_2$ and $Ti(OR)_4$.[6] In this reaction, $Ti(OR)_4$ acts as a basic reagent to enhance the nucleophilicity of the malonate moiety through the formation of a titanium enolate; for example, the reaction of 4-pentynylmalonate **1a** gave iodomethylenecyclopentane *E*-**2a** with high stereoselectivity (*E*/*Z* = 28) through *trans*-addtion of iodine and titanium enolate of malonate across the acetylenic bond (Scheme 1).[7] On the other hand, in the course of this work, we unexpectedly found that when $TiCl_4$ is used instead of $Ti(OR)_4$ and the reaction is conducted under coexistence of $Et_3N$ and $I_2$, *Z*-**2a** is obtained with high selectivity (*E*/*Z* = 1/30) (Scheme 1).

**Scheme 1**



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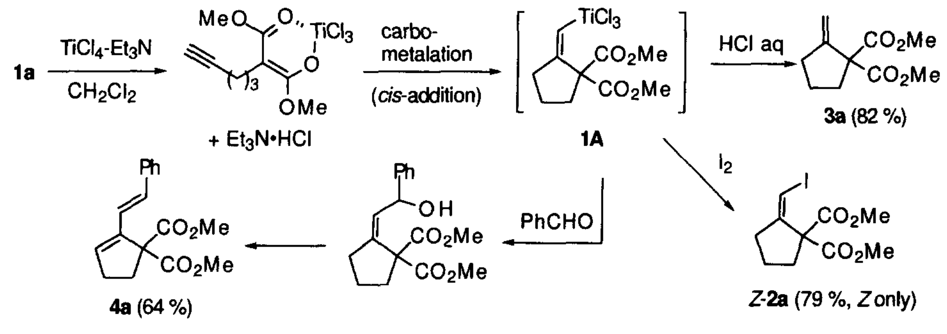
The preferential formation of *Z*-**2a** was assumed to be due to the *cis*-selective intramolecular addition of the trichlorotitanium enolate of malonate to the alkyne and the following stereospecific iodination of the resulting vinyltitanium species. Indeed, the cyclization reaction of **1a** smoothly proceeded even in the absence of $I_2$ to give methylenecyclopentane derivative **3a** in good yield (82 %) after quenching by HCl (Scheme 2).[8,9] In contrast, the cyclized product **3a** could not be obtained by the use of $Ti(O\textit{i}\text{-}Pr)_4$ or $Et_3N$ and $Ti(O\textit{i}\text{-}Pr)_4$. The reaction of **1a** with $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ and $Et_3N$ gave **3a** in a poor yield (21 %); thus, it is obvious that the strong Lewis acidity of the titanium atom is required for the efficient activation of the alkyne part.

It should be noted that, despite the existence of $Et_3N{\bullet}HCl$ in the reaction mixture, the resulting vinyltitanium intermediate **1A** is not protonated and can be further functionalized in a stereospecific manner by the reaction with an electrophile.[10] For example, the reaction of **1A** with $I_2$ exclusively gave iodomethylenecyclopentane derivative *Z*-**2a** (Scheme 2). In addition, C-C bond-forming reaction of **1A** is also possible; that is, the reaction of **1A** with benzaldehyde gave diene **4a** in 64 % through the addition to aldehyde and the following dehydration (Scheme 2).

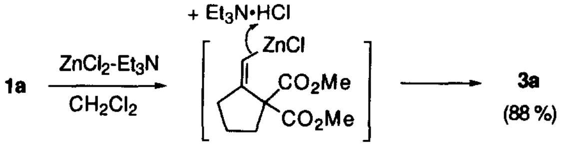
Although prolonged reaction time is required (14 h), the present reaction proceeded even in the absence of $Et_3N$ to give **3a** in good yield (80 %). In this case, however, further functionalization of vinyltitanium intermediate **1A** could not be performed, because during the cyclization reaction a rapid protonation of **1A** by the resulting HCl occurs. Thus, $Et_3N$ acts not only as a basic reagent for the deprotonation but also as an effective HCl scavenger to prevent the protonation of the vinyltitanium intermediate **1A**.

Among the other metallic reagents examined here,[11] the use of $ZnCl_2$ was also effective. The reaction of **1a** with $ZnCl_2$ and $Et_3N$ gave **3a** in good yield (88 %, Scheme 3), while the following iodination of vinylzinc intermediate failed. This result may indicate that the vinylzinc intermediate is easily protonated by $Et_3N{\bullet}HCl$ in the reaction mixture.

**Scheme 2**



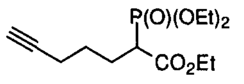
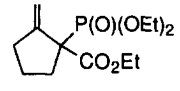
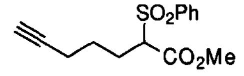
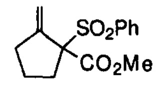
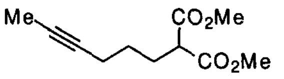
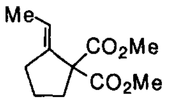
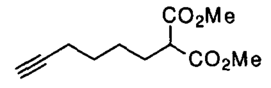
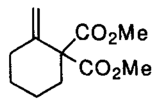
**Scheme 3**



The preliminary results of carbotitanation of various alkynylated active methine compounds are shown in Table 1. Similar to malonate derivative **1a**, the reaction of active methine compounds **1b** and **1c** with phosphonyl and sulfonyl groups also gave the products **3b** and **3c** in good yields (Entries 1,2). This reaction can be also applied to disubstitued alkyne; that is, although the reaction required prolonged time in comparison with those of 1-alkyne **1a**-**1c**, the reaction of 4-hexynylmalonate **1d** gave the product **3d** with complete stereoselectivity (*cis*-addition, Entry 3).[12] On the other hand, in the 6-membered ring-forming reaction with 5-hexynylmalonate **1e**, a considerable decrease in the chemical yield was observed (34 %, Entry 4). In all the reactions shown in Scheme 2 and Table 1, the *exo*-cyclized products were obtained as a single regioisomer without the formation of an *endo*-cyclized product.

**Table 1. Intramolecular Carbotitanation Reaction**[a]

$$\mathbf{1} \xrightarrow[CH_2Cl_2,\ rt]{TiCl_4\text{-}Et_3N} \xrightarrow{HCl\ aq} \mathbf{3}$$

| Entry | 1 | Time (h) | 3 | Yield (%) |
|---|---|---|---|---|
| 1 | <br>**1b** | 1.5 | <br>**3b** | 83 |
| 2 | <br>**1c** | 1 | <br>**3c** | 86 |
| 3 | <br>**1d** | 12 | <br>**3d** (*E* only)[b] | 65 |
| 4 | <br>**1e** | 1 | <br>**3e** | 34 |

[a] Carbotitanation: **1** (1 mmol), $TiCl_4$ (1.8 mmol), $Et_3N$ (1.0 mmol), $CH_2Cl_2$ (8 ml), rt.
[b] *Z*-isomer was not detected by 300 MHz $^1$H-NMR.

In conclusion, we have succeeded in the development of the intramolecular carbotitanation reaction of active methine compounds having an unactivated 4-alkynyl group which proceeds in a highly *cis*-selective manner in the presence of $TiCl_4$ and $Et_3N$. The present reaction should be complementarily used with the iodocarbocyclization reaction of alkynylmalonates as a stereoselective synthetic method of cyclopentanoid compounds with *exo*-olefin.

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5. Kubota, K.; Nakamura, E. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2491-2493.
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7. Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106-3112.
8. Typical procedure of carbotitanation: To alkynylmalonate **1a** (198 mg, 1 mmol) in $CH_2Cl_2$ (8 ml) was added $Et_3N$ (0.14 ml, 1 mmol) and $TiCl_4$ (0.2 ml, 1.8 mmol) under argon atmosphere at rt. After the mixture was stirred for 30 min, $I_2$ (508 mg, 2 mmol) was added, and then the reaction mixture was stirred for 30 min at rt. The mixture was poured into 2% HCl and extracted with $Et_2O$. The $Et_2O$ extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane / AcOEt = 20) gave *Z*-**2a**[7] (256mg, 79 %).
9. Excess of $TiCl_4$ (1.8 eq) to $Et_3N$ is required to get the cyclized product in good yield. Although the reason is not clear, the use of 1.2 eq of $TiCl_4$ and $Et_3N$ resulted in the considerable decrease in the chemical yield due to the formation of unidentified by-products.
10. The resulting **1A** may be stabilized by the intramolecular coordination of two ester groups to the titanium atom. In addition, the formation of the *Z*-vinyltitanium intermediate **1A** is remarkable in contrast with the palladium-catalized carbocylization with **1a**, which exclusively gives the *E*-vinyl palladium species via *trans*-addtion of a palladium and a malonate anion.[2b]
11. In the reaction of **1a** with $Et_3N$ and other metalic reagents such as $BBr_3$, $ZrCl_4$ or $SnCl_4$, the cyclized product **3a** could not be obtained.
12. The stereochemistry of **3d** was determined on the basis of NOE experiment.