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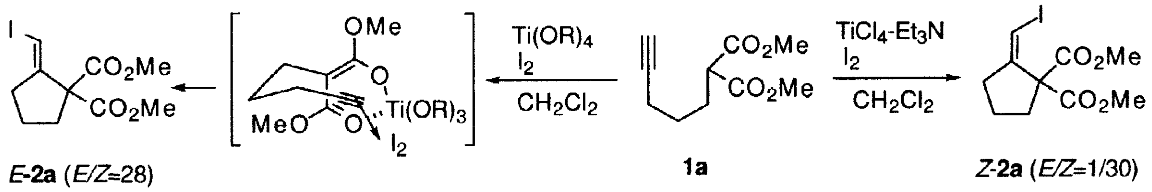
Abstract: In the presence of $TiCl_4$ and Et_3N, intramolecular carbotitanation reaction of active methine compounds having an unactivated 4-alkynyl group proceeds in a highly *cis*-selective manner to give methylenecyclopentane derivatives in good yields.

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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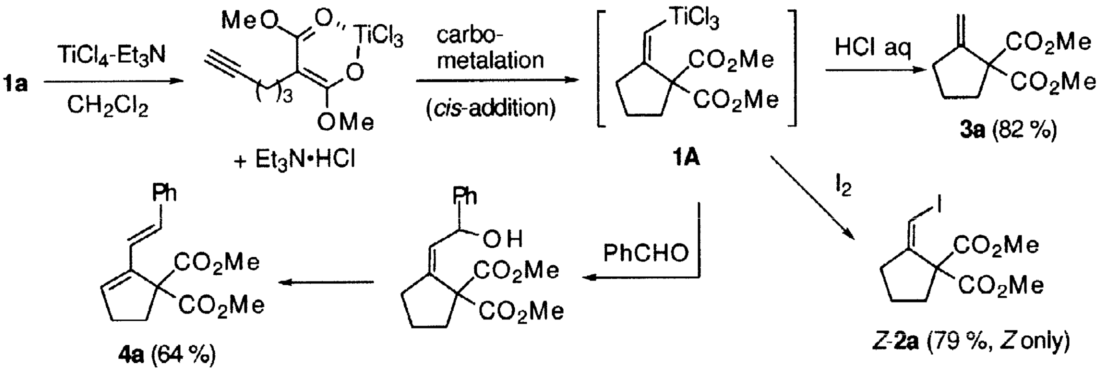
The preferential formation of Z-**2a** was assumed to be due to the *cis*-selective intramolecular addition of the trichlorotitanium enolate of malonate to the alkyne and the following stereospecific iodination of the resulting vinyltitanium species. Indeed, the cyclization reaction of **1a** smoothly 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).

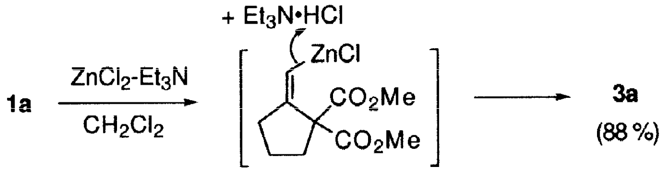
Although prolonged reaction time is required (14 h), the present reaction proceeded even in the absence of Et_3N to give **3a** in good yield (80 %). In this case, however, further functionalization of vinyltitanium intermediate **1A** could not be performed, because during the cyclization reaction a 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



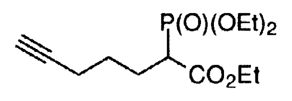
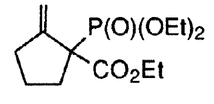
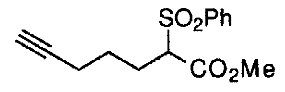
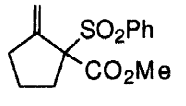
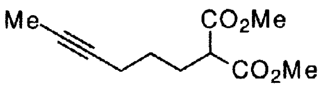
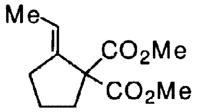
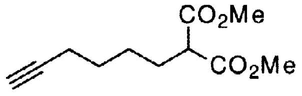
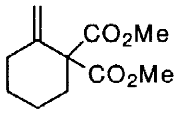
Scheme 3



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]

$$\mathbf{1} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt}]{\text{TiCl}_4\text{-Et}_3\text{N} \qquad \text{HCl aq}} \mathbf{3}$$

Entry	1	Time (h)	3	Yield (%)
1	 **1b**	1.5	 **3b**	83
2	 **1c**	1	 **3c**	86
3	 **1d**	12	 **3d** (*E* only)[b]	65
4	 **1e**	1	 **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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References and Notes

1. (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; New York, Pergamon Press: 1991; Vol. 4, pp 865-911. (b) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080-3090 and references cited therein.
2. Examples of intramolecular carbometalation reaction of enolates with unactivated olefins or alkynes: (a) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1990**, *46*, 7763-7773. (b) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293-6304. (c) Yeh, M-C. P.; Chuang, L-W.; Ueng, C. H. *J. Org. Chem.* **1996**, *61*, 3874-3877. (d) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157-2158. (e) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett*, **1998**, 446-448. (f) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 2442-2450.
3. Examples of intermolecular carbometalation reaction of enolates to unactivated olefins or alkynes: (a) Bertrand, M. T.; Courtois, G.; Miginiac, L. *Tetrahedron Lett.* **1974**, 1945-1948. (b) Ehrhardt, H.; Mildenberger, H. *Liebigs Ann. Chem.* **1982**, 989-993. (c) Stack, J. G.; Simpson, R. D.; Hollander, F. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1990**, 112, 2716-2729. (d) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Syn. Chem. Org. Jpn.* **1996**, *54*, 267-279.
4. Example of palladium-catalyzed addition of activated methylene compounds to allenes: Yamamoto, Y. Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019-6020.
5. Kubota, K.; Nakamura, E. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2491-2493.
6. (a) Taguchi, T.; Kitagawa, O.; Inoue, T.; *J. Syn. Org. Chem. Jpn.* **1995**, *53*, 770-779. (b) Kitagawa, O.; Inoue, T. Taguchi, T. *Rev. Heteroatom Chem.* **1996**, *15*, 243-262. (c) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, 62, 7384-7389 and references cited therein.
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.