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Alkaline Metallic Reagent-Catalyzed Hydrocarbocyclization Reaction of Various Active Methine Compounds Having an Unactivated 4-Alkynyl or Allenyl Group

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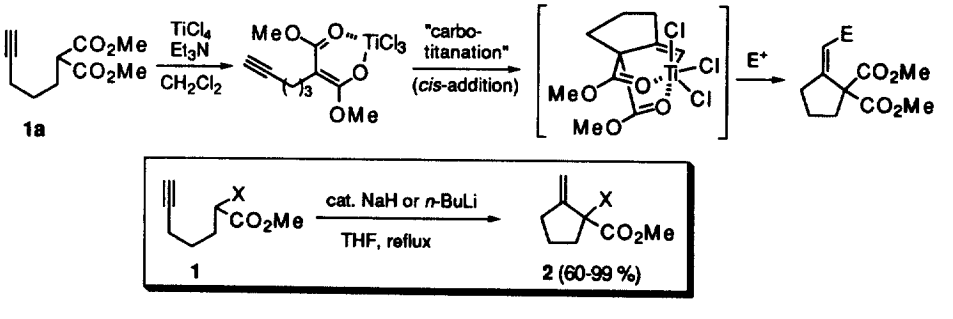
Abstract: On using a catalytic amount of NaH or *n*-BuLi, hydrocarbocyclization reaction of various active methine compounds having an unactivated 4-pentynyl or 3,4-pentadienyl group proceeded through proton transfer mechanism to give methylenecyclopentane derivatives in good yields.

Keywords: cyclization; alkynes; lithium and compounds; catalysis

5-Hexenyl- or 5-hexynyllithium derivatives are well known to smoothly cyclize at room temperature to give carbocyclic alkyl- or alkenyllithium in good yields, respectively.[1] In contrast to the reaction of these nonstabilized carbanions, carbocyclization of typical metal enolates prepared from active methylene compounds having an unactivated C-C π-bond should be difficult to achieve because of the endothermic process involving the conversion of a stabilized enolate anion to an unstabilized carbanion.[2] Such reaction has been generally carried out with assistance of a transition metal catalyst such as Pd, Co, Mo.[3,4] On the other hand, we recently found a carbocyclization reaction of various active methine compounds having unactivated 4-alkynyl or allenyl groups mediated by a Lewis acid such as $TiCl_4$ or $SnCl_4$.[5] The formation of a stabilized intermediate on the basis of intramolecular coordination of two functional groups to the metallic center may be the driving force of the Lewis acid-mediated carbocyclization. However, these reactions are undesirable from the viewpoint of green chemistry because the use of excess Lewis acid (1.8 eq) and Et_3N (1.0 eq) is required to get cyclized products in good yields.

In this paper, we report the result of alkaline metallic reagent-catalyzed hydrocarbocyclization reaction of various active methine compounds having an unactivated 4-pentynyl or 3,4-pentadienyl group. The present reaction proceeds in good yields through a proton transfer mechanism in the presence of a catalytic amount of NaH or *n*-BuLi without the assistance of a transition metal. Quite recently, although a similar hydrocarbocyclization reaction of 4-alkynylated active methines through a proton transfer mechanism has been reported by Balme *et. al.*, in this reaction, the use of a transition metal catalyst such as CuI is also required together with a basic reagent such as *tert*-BuOK.[6]

Scheme 1



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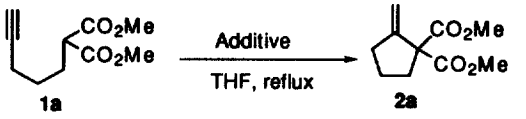
Intramolecular carbometalation reaction of Na- or Li-enolate prepared from 4-pentynylmalonate **1a** with a stoichiometric amount of NaH or *n*-BuLi did not proceed in THF at rt, resulting in the recovery of **1a**. When the THF solution of the Na- or Li-enolate of **1a** was refluxed for 17 h, cyclized product **2a** was obtained in 10 % or 17 % yields, respectively (Table 1, Entries 1,2). On the other hand, we found that when a catalytic amount of an alkaline metallic reagent was used under THF reflux conditions, a remarkable increase in the chemical yield of **2a** was brought about (Entries 3-6). For example, the reaction with 20 mol % of NaH or *n*-BuLi gave product **2a** in 68 % or 74 % yield, respectively (Entries 3,4).

Table 1. Additive Effect in the Hydrocarbocyclization Reaction of 1a[a]



1a **2a**

Entry	Additive	Time (h)	Yield (%)[b]
1	NaH (1.0 eq)	17	10
2	*n*-BuLi (1.0 eq)	17	17
3	NaH (0.2 eq)	17	68
4	*n*-BuLi (0.2 eq)	17	74
5	*n*-BuLi (0.2 eq), $CH_2(CO_2Me)_2$ (0.2 eq)	17	84
6	*n*-BuLi (0.1 eq), $CH_2(CO_2Me)_2$ (0.1 eq)	5	86
7	*tert*-BuOK (0.1 eq)	17	19

[a] Hydrocarbocyclization: **1a** (1 mmol), Additive, THF (5 ml), reflux. [b] Isolated yield.

These results may be explained in accordance with Fig. 1. The intramolecular carbolithiation of Li-enolate **1A** should be a thermodynamically unfavorable process, because a stabilized malonate anion is converted to a non-stabilized vinyl anion. Therefore, the cyclization reaction of **1a** hardly proceeded in the presence of a stoichiometric amount of an alkaline metallic reagent. In contrast, upon using a catalytic amount of *n*-BuLi, since non-stabilized vinyl lithium intermediate **1A'** is irreversibly protonated by the acidic α-hydrogen of pentynylmalonate **1a** to give hydrocarbocyclized product **2a**, the reaction may proceed efficiently and catalytically. Indeed, the addition of dimethyl malonate (0.2 eq) as a proton source led to an increase in the chemical yield of **2a** in comparison with the conditions of entry 4 (84 %, Table 1, Entry 5). The reaction smoothly proceeded even in the presence of 10 mol % of *n*-BuLi and dimethyl malonate to give **2a** in 86 % yield (Entry 6).[7] On the other hand, when 10 mol % of *tert*-BuOK was used as a basic reagent under THF reflux conditions, the considerable decrease in the chemical yield of **2a** was observed (19 %, Entry 7). Thus, as shown in Balme's report, it is obvious that in the reaction with *tert*-BuOK, the addition of transition metal is required to get **2a** in a good yield.[6]

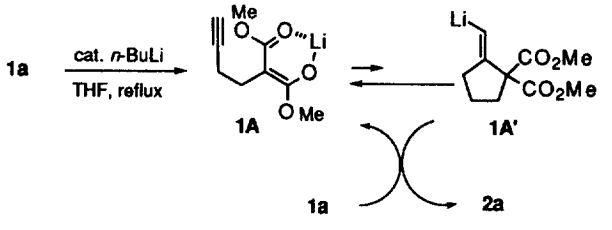
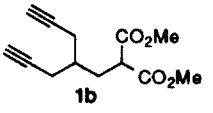
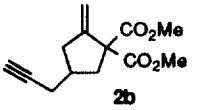
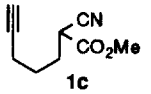
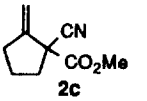
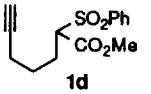
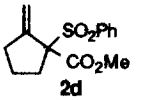
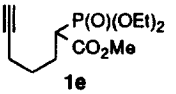
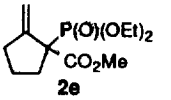
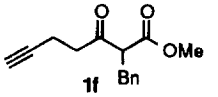
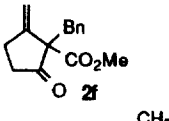
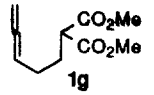
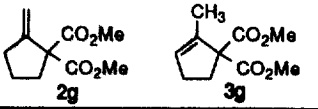


Fig.1. Possible Mechanism of *n*-BuLi Catalyzed Hydrocarbocyclization Reaction.

The hydrocarbocyclization reactions of various 4-pentynyl or 3,4-pentadienyl active methine compounds with 10 mol % of *n*-BuLi were investigated under THF reflux conditions (Table 2).[8] The reaction of bisalkynylated malonate **1b** proceeded without any side reaction at the unreacted 4-alkynyl group

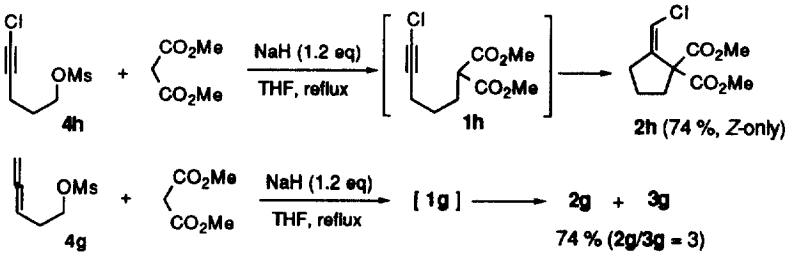
to give product **2b** in a quantitative yield (Entry 1). The reaction of not only malonate derivatives **1a** and **1b** but also cyanoacetate **1c**, sulfonylacetate **1d** and phosphonoacetate **1e** with a 4-pentynyl group gave methylenecyclopentane derivatives **2c-2e** in good yields (Entries 2-4).[9] It should be noteworthy that the reaction of β-ketoester derivative **1f** gave cyclized product **2f** in 60 % yield under the same conditions (Entry 5), while intramolecular carbotitanation reaction of **1f** with $TiCl_4$ and Et_3N[5a,b] did not proceed. In the reactions of 4-pentynyl derivatives **1a-1f**, the formation of a 6-*endo*-cyclized product was not observed; thus, the reaction should proceed in complete 5-*exo*-selectivity. Furthermore, the reaction of allenyl derivative **1g** having a 3,4-pentadienyl group also gave cyclized products in 91 % yield (Entry 6). In this case, **2g** with *exo*-methylene and **3g** with *endo*-olefin were obtained in a ratio of 4 : 1, respectively, through the protonation of the resulting allyl lithium intermediate.

Table 2. *n*-BuLi Catalyzed Hydrocarbocyclization Reaction of Various Active Methines[a]

Entry	1	Product 2 or 3	Yield (%)[b]
1[c]	 **1b**	 **2b**	99
2	 **1c**	 **2c**	79
3	 **1d**	 **2d**	88
4	 **1e**	 **2e**	67
5	 **1f**	 **2f**	60
6	 **1g**	 **2g** **3g**	91 (2g/3g = 4)

[a] Hydrocarbocyclization: **1** (1 mmol), *n*-BuLi (0.1 mmol), THF (5 ml), reflux, 17 h.
[b] Isolated yield. [c] Dimethyl malonate (0.1 mmol) was added as proton source.

Scheme 2



Unfortunately, the hydrocarbocyclization reaction could not be applied to substituted alkynyl derivatives such as 4-hexyny- or 5-pheny-4-pentynylmalonate and 6-membered ring-forming reaction with 5-hexynylmalonate. In these reactions, the starting materials were quantitatively recovered. On the other hand, it was found that chloroalkynyl derivative is more reactive than 4-pentynyl derivatives. That is, the reaction of mesylate **4h** with dimethymalonate (1.5 eq) using NaH (1.2 eq) gave chloromethylene cyclopentane derivative **2h** (74 % yield) in one step without the formation of chloropentynyl malonate **1h** through the substitution of the mesyl group and subsequent hydrocarbocyclization (Scheme 2). The reaction proceeded in a completely *trans*-addition manner to give *Z*-**2h** as a single stereoisomer. This tandem substitution and carbocyclization reaction was also observed in the case of mesylate **4g** with an allenyl group (Scheme 2). In this reaction, similar to the reaction shown in entry 6 of Table 2, cyclized products **2g** and **3g** were obtained in a ratio of 3 : 1 (74 % yield), respectively.[10]

In conclusion, we have succeeded in the development of alkaline metallic reagent-catalyzed hydrocarbocyclization reaction of various 4-pentynyl or 3,4-pentadienyl active methine compounds. It should be noted that the reaction proceeds in the presence of a catalytic amount of cheap NaH or *n*-BuLi without the assistance of any transition metal catalyst. In addition, since the present reaction hardly proceeds in the presence of a stoichiometric alkaline metallic reagent, it may be advantageous as a catalytic reaction.

References and Notes

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4. Carbocyclization of propargyl malonate and *N*-(*o*-ethynyl)malonanilide which proceeds in the presence of slightly excess NaH has been reported. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett*, **1993**, 65-68. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett*, **1998**, 446-448.
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7. Typical procedure of hydrocarbocyclization: To dimethyl 4-pentenylmalonate **1a** (396 mg, 2 mmol) and dimethyl malonate (26 mg, 0.2 mmol) in THF (10 ml) was added 1.54 M *n*-hexane solution of *n*-BuLi (0.13 ml, 0.2 mmol) under argon atmosphere at rt, and then the mixture was refluxed for 5 h. The mixture was poured into water and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane / AcOEt = 40) gave **2a** (340 mg, 86 %).
8. 4-Alkynylated active methines **1a-1f** were prepared according to reported procedures.[3c] See also Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103-10114.
9. In the hydrocarbocyclization reactions of cyanoacetate **1c**, sulufonylacetate **1d** and phosphonoacetate **1e** with a 4-pentynyl group, increase in the chemical yields of **2c-2e** could not be observed by the addition of proton sources such as methyl cyanoacetate, methyl sulfonylacetate and ethyl phosphonoacetate.
10. 3,4-Pentadienylmalonate **1g** was prepared through the reaction of mesylate **4g** and dimethyl malonate in the presence of CsF in DMF.