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A Novel Modified Baylis−Hillman Reaction of Propiolate

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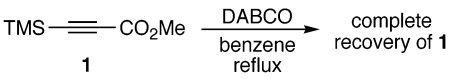
The development of a carbon−carbon bond-forming reaction is one of the most important subjects in synthetic organic chemistry. Among them, the Baylis−Hillman reaction[1] has recently made remarkable progress in the areas of shortening of reaction time,[2] extension of applicability,[1c] and asymmetric induction.[3] This reaction is usually carried out between conjugated carbonyl compounds, typically acrylates, and aldehydes in the presence of tertiary amine or trialkylphosphine as a catalyst, providing α-hydroxyalkylated acrylate systems which are useful precursors for numerous biologically important molecules. However, this reaction still has a serious inherent limitation in applying for the acrylates bearing a substituent(s) on their *β*-position.[4] Thus, alternative approaches to synthesize *β*-branched Baylis−Hillman products have been reported by several groups, which include hydroalumination[5] or titanium complexation[6] of propiolates, followed by addition to aldehydes, and vanadium-catalyzed formation of allenoates from propargyl alcohols.[7] Recently, preparation of *β*-chlorinated Baylis−Hillman products have been reported using conjugated acyl alkynes such as ethynyl methyl ketone and propiolates as a substrate,[8] in which stoichiometric titanium tetrachloride and catalytic chalcogenides were used. Although propiolates cannot be utilized as a substrate for the traditional Baylis−Hillman reaction because of the lack of the α-proton essential to regenerate the catalyst, these examples suggest that propiolates could function at least as an acceptor for the Baylis−Hillman catalyst. In this context, we have examined the reaction of methyl 3-trimethylsilylpropiolate under traditional Baylis−Hillman conditions resulting in the formation of novel *β*-acylated Baylis−Hillman products with high *E,Z*-stereoselectivities, involving simultaneous formation of two C−C bonds. In this communication, we describe the preliminary results of this novel reaction including a new potential method to generate alkylidene carbene species.

(eq. 1)



(eq. 2)

Propiolates have been reported to occur in an amine-promoted dimerization,[9] and in fact the reaction proceeded smoothly in our hands (eq 1). This implies that amine bases such as DABCO cannot be used for the Baylis−Hillman-type reaction of *β*-unsubstituted propiolates. Taking these findings into consideration, we envisioned that the use of *β*-silylated propiolates would suppress the dimerization, leading to a new Baylis−Hillman-type reaction of propiolates as a result of the migration of the silyl group. As a preliminary experiment, we confirmed that methyl 3-trimethylsilylpropiolate (**1**) did not change in the presence of DABCO even in refluxing benzene (eq 2).

Scheme 1

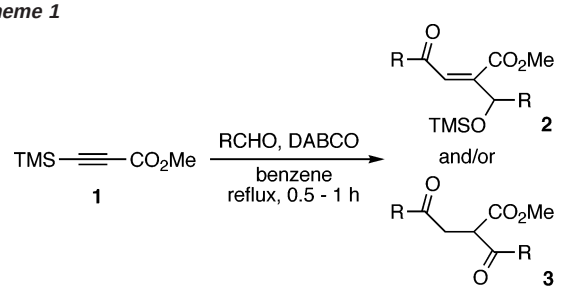


Table 1. Reaction of Propiolate (**1**) with Aromatic Aldehyde in the Presence of DABCO[a]

entry		R	yield (%)[b]	ratio (**2**:**3**)[c]
1	**a**	Ph	73	74:26
2	**b**	2-Me-C_6H_4	56	100:0
3	**c**	3-Me-C_6H_4	64	78:22
4	**d**	4-Me-C_6H_4	78	78:22
5	**e**	2-MeO-C_6H_4	quant.[d]	100:0
6	**f**	3-MeO-C_6H_4	50	76:24
7	**g**	4-MeO-C_6H_4	83	83:17
8	**h**	4-Cl-C_6H_4	43	37:63
9	**i**	1-naphthyl	44	100:0
10	**j**	2-naphthyl	72	63:37
11	**k**	2-Br-4,5-$(MeO)_2$-C_6H_2	51	100:0

[a] The reaction was carried out with 0.5 mmol of aldehyde, 1 mmol of propiolate, and 1 mmol of DABCO in benzene (1 mL) under Ar atmosphere. [b] Isolated yields (**2** + **3**) based on aldehyde. [c] These products could be separated by column chromatography. [d] Isolated in a desilylated form.

However, when this reaction was carried out in the presence of benzaldehyde, a complete consumption of the aldehyde was observed to give *β*-acylated and TMS-masked Baylis−Hillman adduct **2** concomitant with **3** as a minor product (Scheme 1). The results for several aromatic aldehydes are listed in Table 1 in which no *E*-isomers of the product **2** were detected in all cases.[10] Not only simple benzaldehyde but also a multisubstituted one and naphthaldehydes were also available for the reaction.[11] These products containing important functional groups can subsequently be manipulated with a variety of transformations. Thus, this novel reaction potentially provides a new approach for preparation of such multifunctionalized olefins in a stereoselective manner.

Prolonged reaction time caused a change in the product ratio, resulting in an increasing yield of **3**. In addition, when isolated **2** was subjected to the same reaction conditions, gradual conversion to **3** was observed. Thus, the product **3** could be formed from **2**, probably via isomerization of the double bond followed by hydrolysis of the resulting silyl enol ether. This is supported by the results (Table 1, entries 2, 5, 9 and 11) in which the ortho substituted benzaldehydes did not yield the compound **3** because of inefficiency of the isomerization due to the steric repulsion between the ortho substituent and allylic substituents.

On the other hand, aliphatic aldehydes gave an alkyne product (**4**), and compounds **2** and **3** could not be detected (Scheme 2).

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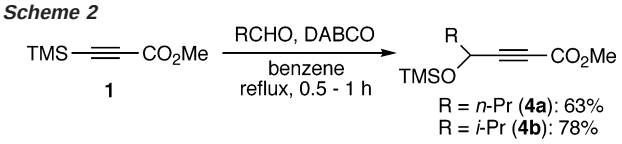
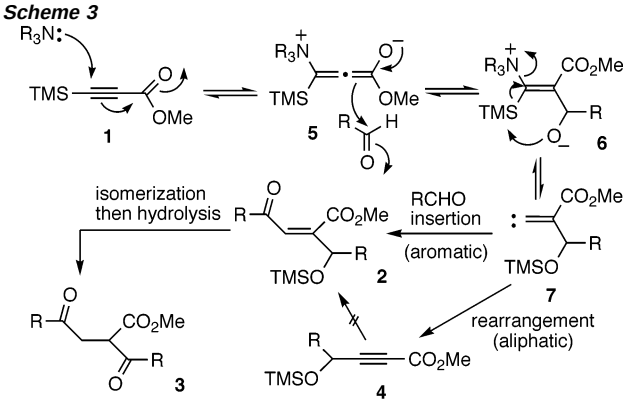
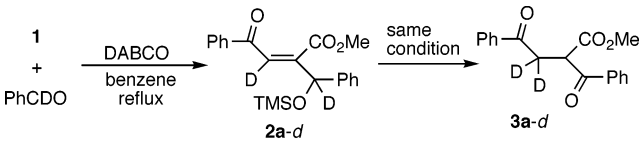
Scheme 2



Scheme 3



Scheme 4



This finding is in contrast with the results from aromatic aldehydes which afforded no such alkyne products.

Although the reaction mechanism has not yet been confirmed with sufficient evidence, we suppose that this new reaction involves an intermediacy of alkylidene carbene species (**7**) which might originate from the standard Baylis−Hillman mechanism and migration of the TMS group (Scheme 3).[12,13] Alkylidene carbenes are known as very reactive species and are reported to undergo dimerization, rearrangement to alkynes, or insertion reaction.[14,15] In our reaction system, rearranged product **4** could be formed only in the case of aliphatic aldehydes. It was revealed that compound **4** (R = Ph), prepared in an alternative way,[16] was rapidly decomposed to afford a complex mixture when treated with benzaldehyde and DABCO. Thus, the reaction pathway leading to the product **2** would not include **4** as an intermediate and can be rationalized by postulating a direct C−H insertion process.[17,18] This reaction mechanism is also supported by experimental results using deuterated benzaldehyde as a starting material (Scheme 4).[19,20]

In this communication we disclosed a new reaction of propiolates and aldehydes mediated by DABCO, analogous to the Baylis−Hillman reaction, which resulted in the formation of novel β-functionalized Baylis−Hillman adducts. It was also suggested that the reaction could provide a new methodology for the generation of alkylidene carbene species. Further investigation of the reaction mechanism and synthetic application of the reaction are now in progress.

Supporting Information Available: Experimental procedures and spectral data for compound **2**, **3**, and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34179q. (c) Recent excellent review: Ciganek, E. *Org. React.* **1997**, *51*, 201.

(2) (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (b) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun.* **1996**, 2713. (c) Aggarwal, V. K.; Mereu, G. J.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (d) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612. (e) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413. (f) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.

(3) (a) Brzezinsky, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (b) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (d) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030. (e) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867. (f) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015. (g) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (h) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.

(4) (a) Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *48*, 6371. (b) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807.

(5) (a) Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 1624. (b) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037. (c) Li, G.; Wei, H.-X.; Willis, S. *Tetrahedron Lett.* **1998**, *39*, 4607. (d) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979.

(6) Suzuki, D.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3290.

(7) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230.

(8) (a) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358. (b) Wei, H.-X.; Gao, J. J.; Li, G. *Tetrahedron Lett.* **2001**, *42*, 9119.

(9) (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952. (b) Acheson, R. M.; Ansell, P. J.; Murray, J. R. *J. Chem. Res. (S)* **1986**, 378. (c) Medion-Simon, M.; Pindur, U. *Helv. Chim. Acta* **1991**, *74*, 430.

(10) The geometry was determined by an NOE experiment between the olefinic proton and the methyne proton bearing a trimethylsilyloxy group.

(11) Highly electron-deficient aldehydes such as 4-nitro or pentafluorobenzaldehyde afforded a complex mixture under the reaction conditions.

(12) According to this mechanism, DABCO should act in a catalytic fashion. Using 10 mol % of DABCO, however, the product yield decreased considerably, although the yield % was over the amount of DABCO.

(13) Recently, it was reported that the reaction of aromatic aldehydes, DMAD, and catalytic pyridine gave 2-oxo-3-benzylidenesuccinates via oxetene intermediate. However, in our reaction, the product(s) based on this mechanism could not be detected, probably due to predominance of silyl migration over the formation of strained oxetene ring. See; Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495.

(14) Reviews on nature and reactivity of alkylidene carbene: (a) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348. (b) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.

(15) Recent reports on generation of alkylidene carbene and their applications: (a) Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *Tetrahedron Lett.* **2001**, *42*, 8575. (b) Feldman, K. S.; Perkins, A. L. *Tetrahedron Lett.* **2001**, *42*, 6031. (c) Tobe, Y.; Iwasa, N.; Umeda, R.; Sonoda, M. *Tetrahedron Lett.* **2001**, *42*, 5485. (d) Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* **1995**, *36*, 8843. (e) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721. (f) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135.

(16) This compound was synthesized by treatment of methyl propiolate with LDA followed by benzaldehyde and trimethylsilyl chloride, successively.

(17) For the reaction of carbene with aldehydes; (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. (b) L'Esperance, R. P.; Ford, T. M.; Jones, M., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 209. In these reports, formation of oxirane or dioxorane via carbonyl ylide is described. Thus, the reaction described here is the first example of direct C−H insertion of aldehyde into a carbene to our best knowledge.

(18) Although it seems that the stereochemistry of the product **2** is regulated in this last step, it remains unclear what caused the exclusive selectivity. As another possibility, the selectivity might be controlled thermodynamically via *E-Z* isomerization, not kinetically.

(19) In a recent report on the acylation of vinylselenonium ylide with aldehydes, it is described that benz(aldehyde-*d*) did not give the deuterated product. This implies that the mechanism of our reaction is different from that proposed in the literature, which includes allenoate intermediate, not via alkylidene carbene. See; Watanabe, S.; Kusumoto, T.; Yoshida, C.; Kataoka, T. *Chem. Commun.* **2001**, 839.

(20) For experimental detaild and spectral data, see Supporting Information.

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