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Carbon−Carbon Bond-Forming Reaction of Cyclic Sulfonium Ylides Stabilized by a Carbonyl Group

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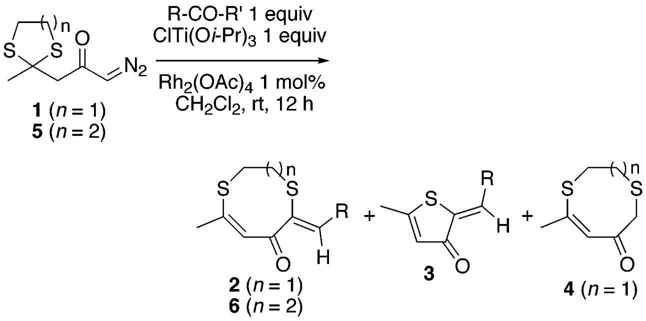
Received February 4, 2004

Abstract: Rhodium(II)-catalyzed decomposition of diazoketones **1** and **5** bearing a cyclic dithioacetal, in the presence of aldehyde and ClTi(O*i*-Pr)$_3$, afforded both or one of the C═C-bonded products, i.e., ring-enlarged enone **2** and ring-transformed thiophenone **3**, that were formed between aldehyde and intermediate bicyclosulfonium ylide. The stereochemistry of the exocyclic C═C bond in the products was exclusively *Z*. The sulfonium atom that transiently composed the ylide was incorporated into products, but no oxirane was formed.

Among onium ylides utilizable for carbon−carbon (C−C) bond-forming reactions in organic synthesis,[1−3] the profile of sulfonium ylides (*S*-ylide) is represented by the Corey−Chaykovsky reaction that is readily utilized for oxirane synthesis.[4] However, the reactions of cyclic *S*-ylides, particularly of bicyclic ylides,[5] are scarcely reported despite the expected applicability to constructing rather complex sulfur-containing molecular frameworks. Additional concern with the ylides is the low reactivity of carbonyl-stabilized homologues.[6]

TABLE 1. Rh(II)-Catalyzed Reactions of 1 and 5 with Carbonyl Compounds in the Presence of ClTi(O*i*-Pr)$_3$[a]



entry	diazoketone (n)	carbonyl compounds[d]			products (%)			
		R	R′		**2**	**3**	**4**	**6**
1[b]	**1** (1)	Ph	H	(a)			74	
2	**1** (1)	Ph	H	(a)	22	55		
3[c]	**1** (1)	Ph	H	(a)	54		trace	
4	**1** (1)	styryl	H	(b)	60	3		
5	**1** (1)	PhCH$_2$CH$_2$	H	(c)	60		trace	
6	**1** (1)	Ph	Me	(d)			45	
7	**1** (1)	Ph	CF$_3$	(e)			70	
8	**5** (2)	Ph	H	(a)		63		26
9	**5** (2)	styryl	H	(b)		8		64

[a] Reactions were carried out under N$_2$. Concentration: 1.0 mmol of diazoketone/10 mL of CH$_2$Cl$_2$. [b] Without ClTi(O*i*-Pr)$_3$. [c] Ti(O*i*-Pr)$_4$ was used as a Lewis acid. [d] (a) Benzaldehyde, (b) cinnamaldehyde, (c) 3-phenylpropanal, (d) acetophenone, (e) 2,2,2-trifluoroacetophenone.

Recently, we have unveiled a novel C−C bond-forming reaction of cyclic ethereal oxonium ylides that are generated from the rhodium(II)-catalyzed reaction of diazoketones bearing a cyclic ethereal ring, with carbonyl compounds on the carbanion center.[7,8] In the reaction, use of titanium salts as a Lewis acid was essential for not only activating the carbonyl electrophiles but also stabilizing the short-lived keto-ylide intermediates without interrupting the ylide generation.

On a similar mechanistic basis, we expected that the Rh(II)-catalyzed reaction of diazoketones bearing a cyclic or an acyclic sulfide group would realize the C−C bond-forming reaction of *S*-ylides stabilized by a carbonyl group. This is a hitherto unknown type of reaction. The present paper reports the results.

As the model substrate of the reaction, cyclic dithioacetals **1** and **5** tethered to a diazoacetonyl side chain were chosen because bicyclic *S*-ylides of type **7** were expected to be generated from them.[9] The Rh(II)-catalyzed reactions of diazoketones **1** and **5** were carried out in the presence of carbonyl compounds and a stoichiometric amount of titanium compound. Results are summarized in Table 1.

In the beginning, reaction of **1** with benzaldehyde (**a**) in the absence of ClTi(O*i*-Pr)$_3$ was examined as a standard reaction to observe the effect of Lewis acid, and it was shown that ring-enlarged eight-membered cyclic enone **4** was the sole product (Table 1, entry 1). In contrast, similar reaction of **1** in the presence of ClTi(O*i*-Pr)$_3$ yielded two C−C-bonded products **2a** and **3a** in an overall yield of 77% (entry 2), both possessing a

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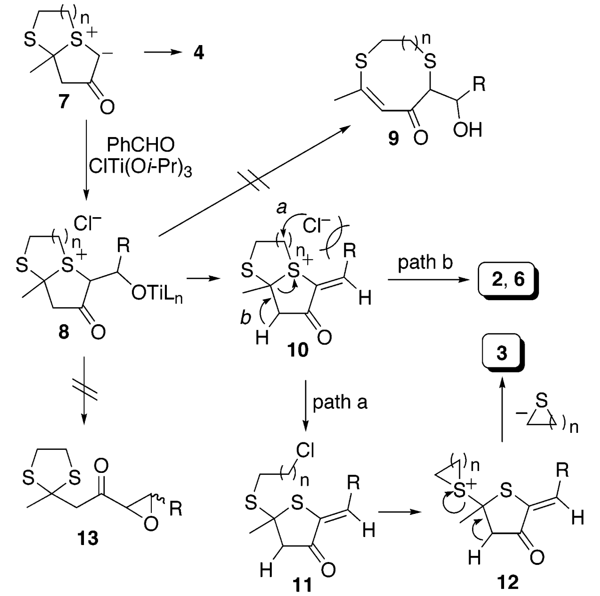
10.1021/jo0498009 CCC: $27.50 © 2004 American Chemical Society

SCHEME 1. Plausible Mechanism of C−C Bond Formation



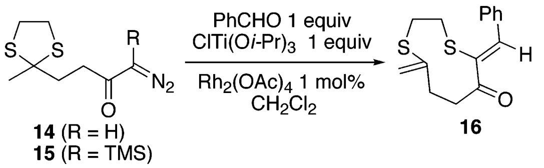
Z-configuration at the newly formed alkylidene bond. When Ti(O*i*-Pr)$_4$ was used as a Lewis acid instead of ClTi(O*i*-Pr)$_3$, C−C-bonded ring-expansion product **2a** was exclusively formed (entry 3). Similarly, highly stereoselective as well as chemoselective formation of **2a** holding an exo alkylidene bond was again observed with cinnamaldehyde (**b**) and 3-phenylpropanal (**c**) (entries 4, 5, and 9). However, with acetophenones (**d** and **e**), the alkylidene bond formation did not take place and cyclic enones **4** were the products (entries 6 and 7). The reaction of diazoketone **5**, bearing a larger 1,3-dithiane moiety than **1**, gave a similar result to that of entry 2 (entry 8). In the reactions shown in Table 1, an epoxy product, which was expected if the Corey−Chaykovsky reaction took place, was not formed.

In the structures of both **2** and **3**, the configuration of the newly formed exo alkylidene bond was exclusively *Z*. This assignment was supported by the X-ray crystallographic analysis (see Supporting Information).

The profile of the present reaction is different from those previously known for the reaction of *S*-ylides with an aldehyde: first, a capto-dative-substituted exo alkylidene bond is formed, although *S*-ylides stabilized by a carbonyl group are known not to undergo attack by a carbon electrophile, while nonstabilized ylides do react to form oxiranes; second, the sulfonium atom of the ylide remains in the product, which is not the case of the Corey−Chaykovsky reaction.

A plausible mechanistic explanation for the present unique reaction is shown in Scheme 1. Although the nucleophilicity of *S*-ylide **7** is low because it is stabilized by the carbonyl group, the ylide can react with the aldehyde activated by a Lewis acid to form sulfonium ion **8**. In **8**, the methyne hydrogen existing between the carbonyl and sulfonium groups is acidic enough to undergo a fast elimination in conjunction with the adjacent titanoxy group. This facile elimination seems to be the main factor prohibiting the formation of epoxide **13** or aldol-type product **9**, which was the case with *O*-ylides.[8]

SCHEME 2. Reaction of Benzaldehyde with Diazoketones 14 and 15 Bearing a Longer Chain in the Presence of ClTi(O*i*-Pr)$_3$



The *Z*-selectivity in the formation of the alkylidene bond may be accounted for on a basis similar to that for the syn selectivity in the Ti-catalyzed aldol reaction[10] and also for *O*-ylides.[8]

Another characteristic feature of the present reaction is that a fragmented five-membered product **3** was formed from both **1** and **5** when ClTi(O*i*-Pr)$_3$ was used as the Lewis acid (Table 1). Its formation was suppressed, however, in the reactions of **1** with 3-phenylpropanal (**c**) (entry 5), with benzaldehyde (**a**) when Ti(O*i*-Pr)$_4$ was used instead of ClTi(O*i*-Pr)$_3$ (entry 3), and nearly suppressed with cinnamaldehyde (**b**) (entry 4). A similar result was observed in the reaction of **5** with cinnamaldehyde (**b**) (entry 8). On the basis of this observation, a possible mechanistic pathway leading to **3** via ring-transformed intermediates **11** and **12** is proposed in Scheme 1. Here, the chloride ion derived from ClTi(O*i*-Pr)$_3$ may play a key role in two ways: (1) it functions as a nucleophile to attack sulfonium ion **10** at the α-position of dithiolane ring ($n = 1$) to yield ring-transformed C−C-bonded product **11** (path a); (2) when aldehyde has a bulky substituent R that interferes with the above-mentioned nucleophilic attack, Cl$^-$ will accept a proton from the position α to the carbonyl group, which is synchronized with the cleaving of the central bond of **10** to give ring-enlarged enone products **2** and **6** (path b). This trend was commonly observed in at least two cases bearing different sizes of the dithioacetal ring (compare entries 8 and 9).

The tether length between the diazo and sulfide moieties does not seem to be restricted to only the three carbons of acetonyl group. When the Rh(II)-catalyzed reactions of diazoketones **14** and **15** were carried out under conditions similar to those employed for **1** and **5**, expected C−C-bonded product **16** was obtained but only in low yields (11 and 17%, respectively). Assuming that elongation of the tether will disfavor intramolecular formation of *S*-ylide versus intermolecular pathways, the reaction was carried out under diluted conditions (concentration of diazoketone was changed from 0.1 to 0.05 mol/L). Indeed, the assumption worked as expected, and product **16** was obtained in 60% yield from **14** (Scheme 2). On the other hand, TMS-substituted diazoketone **15**, which was expected to suppress intermolecular side reactions,[11] improved the yield of **16** only slightly (17%).

Although the present study has unveiled a novel reactivity profile of *S*-ylides, the cyclic moiety of model substrates **1**, **5**, **14**, and **15** may limit the scope of applicability of the reaction. It also brings about the

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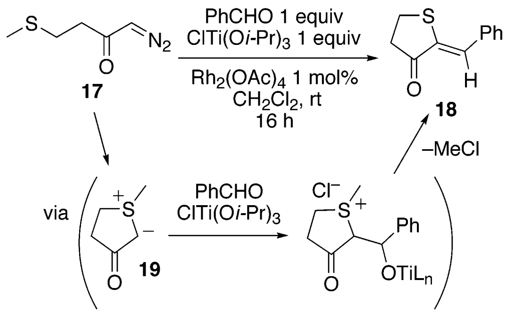
SCHEME 3. C-C Bond-Forming Reaction of Monocyclic Sulfonium Ylide



problem of chemoselectivity between ring-enlargement and ring-transformation pathways, for example, **2** versus **3**. The problem seems to arise from the formation of bicyclic ylide **7** as the common precursor of both products. If five-membered product **3** or its dihydro analogue (for example, **18**) is the target, we thought that the problem might be solved by designing a monocyclic *S*-ylide intermediate. In general, five-membered cyclic *S*-ylides are known to be unstable and easily undergo splitting to ethylene and a vinyl sulfide. Therefore, they are not used for the Corey−Chaykovsky reaction.[5b] Nevertheless, if a monocyclic *S*-ylide with a carbonyl function can be designed, for example, **19**, it may gain moderate stability and reactivity to undergo an aldol-type reaction with activated aldehydes. On the basis of this assumption, diazoketone **17** was designed.

Indeed, the reaction of **17** afforded the expected C−C-bonded cyclic product **18** in 60% yield (Scheme 3). This is the first example of five-membered *S*-ylides that reacted with an aldehyde to form a C−C bond.

To summarize, ketosulfonium ylides that have been thought to be stable enough not to react with aldehydes are proven to be capable of forming an alkylidene bond, provided that the aldehyde is activated by a Lewis acid of a titanium compound. Products are cyclic sulfides bearing a stereoselectively formed exo double bond, and in products structures, the sulfur atom that transiently composes the *S*-ylide is retained. Thus, the profile of the reaction is entirely different from reactions previously known and the overall outcome is the formation of sulfur-containing heterocycles.

Acknowledgment. We thank Mrs. Ikuko Kamada for the X-ray crystallographic analysis.

Supporting Information Available: General methods and detailed experimental procedures for the reactions of diazoketones; ^1H, ^{13}C, and HRMS data for diazoketones **15** and **17** and products **2**, **3**, **6**, **16**, and **18**; and the crystallographic solid structure of products **2a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0498009