[1,5]-H Shift of Aldehyde Hydrogen in Dienal Compounds to Produce Ketenes
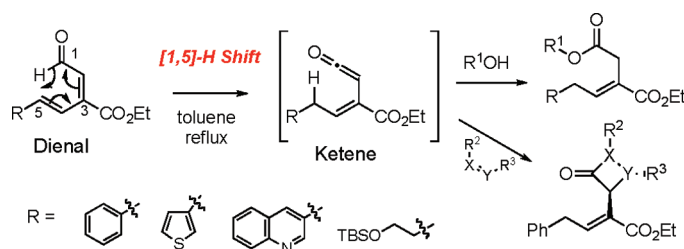
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ABSTRACT

In 3-ethoxycarbonyl-2,4-dienal compounds, a thermal [1,5]-H shift of aldehyde hydrogen easily proceeded to produce the corresponding vinyl ketenes due to the remarkable substituent effect caused by the C3 ester group. The produced ketenes were captured by an alcohol and olefins to afford the corresponding esters and four-membered ring compounds, respectively.

The thermal [1,5] sigmatropic rearrangement is one of the typical pericyclic reactions, and usually called [1,5]-H shift because the moving atom in most cases is hydrogen.[1] As representative examples of such a thermal sigmatropic rearrangement, the [1,5]-H shifts in 2-deutero-6-methyl-2,4-octadiene and cyclopentadiene derivatives have been described.[2] In the case of methylcyclopentadiene, the smooth rearrangement proceeds at room temperature to produce three regioisomers.[2b] Recently, the [1,5]-H migration was applied in some cascade reactions to construct the designed ring systems.[3,4] Although many examples of the

[1,5]-H shift have been reported, most of the rearranging hydrogens are the reactive benzylic or allylic ones attached to an sp[3] carbon.[1a] Meanwhile, the rearrangement of the hydrogen attached to an sp[2] carbon, such as vinyl[5] and aldehyde, is quite rare. In particular, the migration of an aldehyde hydrogen appears unfavorable because the resulting product is rather thermodynamically unfavorable ketene. To the best of our knowledge, the thermal [1,5]-H shift of an aldehyde hydrogen could only be found in three papers. The first example was postulated in the flash pyrolysis of 3,4-epoxycyclopentene (Scheme 1A). The flash pyrolysis of this epoxide (410 °C, 1 Torr, 0.1 s.) would produce 2,4-pentadienal, which would rearrange into the corresponding ketene via the thermal [1,5]-H shift and then trapped with methanol to give the corresponding methyl ester.[6a] The second example was described for the thermal isomerization of β-ionylideneacetoaldehyde (Scheme 1B).[7] It was reported that simple distillation *in vacuo* of this dienal produced the tricyclic cyclobutanone derivatives through an initial *E* to *Z*- isomerization of the double

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Scheme 1. Examples of [1,5]-H Shift of Aldehyde Hydrogens

(A) 2,4-Pentadienal

(B) β-Ionylideneacetoaldehyde

(C) Zincke aldehyde
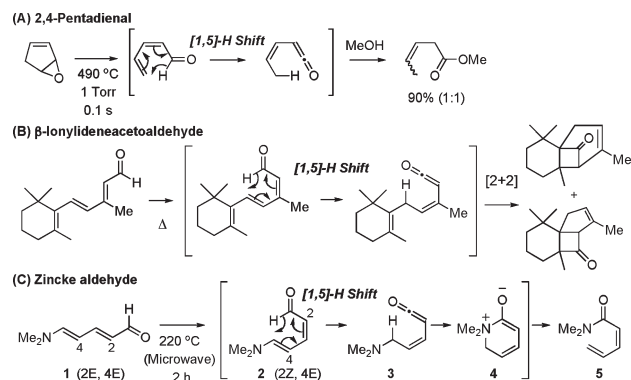
bond adjacent to the carbonyl group, followed by the [1,5]-H shift of the aldehyde hydrogen and the intramolecular [2 + 2] cycloaddition of the resulting ketene with the cyclohexene double bond. The last one was recently reported by the group of Houk and Vanderwal (Scheme 1C).[8] The thermal reaction of (5-(dialkylamino)-2,4-pentadienals (Zincke aldehydes, **1**) (> 160 °C, microwave irradiation) afforded Z-α,β,γ,δ-unsaturated amides **5** through several cascade rearrangements, in which an initial double bond isomerization followed by the thermal [1,5]-H shift of the aldehyde hydrogen produced the intermediary ketene that was subsequently trapped by the intramolecular amino group and then underwent ring-opening, was postulated based on the detailed mechanistic study using quantum mechanical methods. As shown in these examples, it is not easy to utilize the ketene formation via the thermal [1,5]-H shift of an aldehyde hydrogen as a synthetic method because of the requirement of unusual conditions for it and the thermodynamic instability of the resulting ketene.

Scheme 2. [1,5]-H Shift
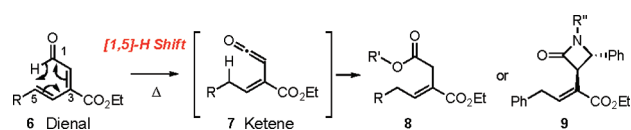
We now describe the thermal [1,5]-H shift of aldehyde hydrogens based on the substituent-driven acceleration effect to produce the corresponding ketenes **7** under a milder condition than previous reports, which are successfully captured by appropriate alcohols and olefins to produce esters **8** with various C5-substituents and four-member ring compounds such as β-lactam **9**, respectively (Scheme 2).

Over the past 10 years, we have developed efficient synthetic methods for multisubstituted pyridines and chiral piperidine compounds based on the rapid 6π-azaelectrocyclization from 1-azatrienes due to the remarkable accelerating effect of its substituents that we had originally discovered (Scheme 3A).[9] For instance, the one-pot synthetic protocol from three easily available components in the presence of Pd(0) catalyst enabled us to obtain the 2-arylpyridine derivatives in high yield.[9k] In this reaction, the key azaelectrocyclization step is dramatically accelerated by the C-4 ester substituent in the azatriene **10** due to the enhancement of the HOMO−LUMO interaction in the 6π-electron system.

**Scheme 3.** Development of One-pot 6π-Azaelectrocyclization and Discovery of Mild [1,5]-H Shift

(A) One-pot Pyridine Synthesis

(B) [1,5]-H Shift
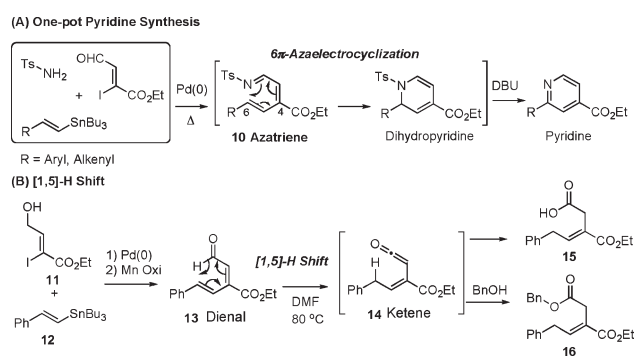
To investigate the role of a palladium catalyst for the imine formation step in the one-pot pyridine synthesis, the phenyl dienal **13**, which was the precursor of the azatriene **10** and was easily prepared *in situ* by coupling between vinyl iodide **11** and vinyl stannane **12**, was heated at 80 °C in DMF without a Pd catalyst. Surprisingly, we obtained the unexpected carboxylic acid **15** as the major product (Scheme 3B). Furthermore, the ester derivative **16** was produced by heating in the presence of benzyl alcohol. We postulated that the reaction must be through ketene **14** as an intermediate, which would be an unprecedented mild condition for its formation from aldehyde. We then investigated this ketene forming reaction including the reactivity and the generality.

First, we optimized the reaction conditions (Table 1). Using *p*-methoxybenzylalcohol (PMBOH) as a trapping

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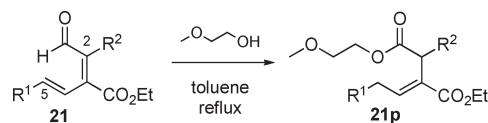
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Table 1. Investigation of the Reaction Condition
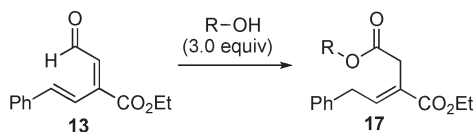
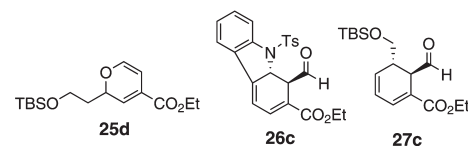

entry	ROH	solvent	temp	time	product	yield / %
1	PMBOH	DMF	100 °C	2 h	**18**	24
2	PMBOH	1,4-Dioxane	reflux	4 h	**18**	47
3	PMBOH	MeCN	reflux	8 h	**18**	27
4	PMBOH	toluene	reflux	3 h	**18**	62
5	BnOH	toluene	reflux	3 h	**16**	65
6	MeO / MeO benzyl-OH	toluene	reflux	3 h	**19**	58
7	MeO-CH2CH2-OH (10 mL / mmol)	toluene	reflux	3 h	**20**	78

reagent of the ketene, we searched for the best solvent and temperature. In a polar solvent such as DMF, 1,4-dioxane and acetonitrile at 100 °C, the corresponding ester products were obtained in 24, 47 and 27% yields, respectively (Entries 1, 2 and 3). We found that toluene under reflux condition gave the best results (Entry 4). We next investigated the alcohol to trap the generated ketene. Though the benzyl alcohol derivatives gave similar results (Entries 5 and 6), 2-methoxyethanol gave the best result in 78% yield, which has a sufficiently high boiling point (124 °C) (Entry 7). Thus, we established the reaction conditions.

We next tested the generality of this thermal ester forming reaction from dienal **13** by changing the substituent at the C5 position. The results are shown in Table 2. The rearrangement of the dienal derivatives substituted at the C5 position with 3-thiophene, 3-pyridine and 3-quinoline smoothly proceeded to produce the corresponding esters **22p**, **23p** and **24p** in 83, 73 and 44% yields, respectively (Entries 2, 3 and 4). Siloxyethyl derivative **25**, which exists as dihydropyrane **25d** resulting from the oxoelectrocyclization of dienal **25**, also afforded the expected product (Entry 5). The 3-indole derivative also produced the desired product **26p** in 56% yield along with a byproduct **26c**, which would be produced by *E*- to *Z*-isomerization of the 4,5-double bond followed by 6π-electrocyclization in 18% yield (Entry 6). In the case of alkenyl substrate **27**, the similar 6π-electrocyclization product **27c** was obtained in 35% yield as the major product. Meanwhile, compound **28** having a bulky alkenyl group gave the rearranged product **28p** via the [1,5]-H shift (Entry 8). Moreover, the tetrasubstituted compound with an ethyl group at C2 also produced the corresponding rearranged product **29p** in good yield, though the reaction rate was slower than that of the trisubstituted compounds (Entry 9). The obtained results strongly suggested that the aldehyde hydrogen of

Table 2. Generality at C5 and C2 Positions

| entry	substrate	product	R[1]	R[2]	time / h	yield / %	byproduct
1	**13**	**20**	phenyl	H	3.0	78	
2	**22**	**22p**	3-thiophene	H	4.0	83	
3	**23**	**23p**	3-pyridine	H	3.0	73	
4	**24**	**24p**	3-quinoline	H	4.5	44	
5	**25**[a]	**25p**	TBSO-CH2CH2	H	3.0	77	
6	**26**	**26p**	3-indole (N-Ts)	H	3.0	56	**26c** : 18%
7	**27**	**27p**	TBSO-alkenyl	H	5.0	-	**27c** : 35%
8	**28**[b]	**28p**	dimethylcyclohexenyl	H	1.0	90	
9	**29**	**29p**	phenyl	Et	14.5	78	

25d **26c** **27c**

[a] The substrate exists as a ring-closed form, **25d**. [b] Methyl ester derivative at C4 was used.

dienal with various C5 substituents successfully rearranged to the C5 position to produce the intermediary ketene, which was captured by the alcohol to produce the corresponding esters efficiently. In some cases, this novel [1,5]-H shift of the aldehyde hydrogen could prevail over the isomerization-electrocyclization.

To broaden the utility of this facile ketene forming reaction, we then tried the Staudinger ketene cycloaddition, namely, the [2 + 2] cycloaddition (Scheme 4). Thus, heating phenyl dienal **13** with butylvinylether under the established reaction conditions afforded the expected cyclobutanone **30** via a [2 + 2] cycloaddition between the double bond of ketene and the vinylether. In the case of phenylimine reactants such as *N*-phenyl-, *N*-methyl- and *N*-benzylimines, the corresponding β-lactam products **31**, **32** and **33** were obtained in 76, 71 and 81% yields, respectively. The stereochemistry of these products were determined by the detailed NMR analysis. Furthermore, heating with azo-compounds (DEAD and DIAD) yielded the corresponding 1,2-diazetidin-3-one **34** and **35** in 56 and

47% yield, respectively. These results obviously demonstrated the ketene formation via the [1,5] sigmatropic rearrangement of the aldehyde hydrogen and that this rearrangement could be useful as the novel one-pot preparation method of various substituted cyclobutanones and azacyclobutanones.

**Scheme 4.** [2 + 2] Cycloaddition of Intermediary Ketene **14**
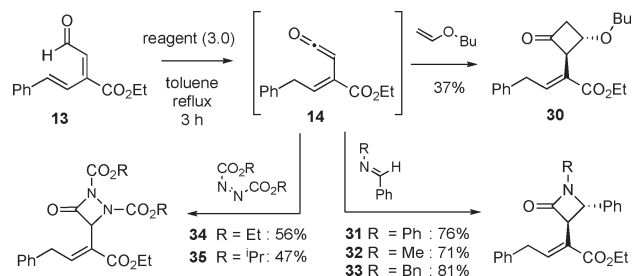
Quite recently, Houk and Vanderwal reported the transformation of Zincke aldehyde **1** to Z-α,β,γ,δ-unsaturated amide **5** by microwave irradiation (Scheme 1C).[8a] They tried to elucidate the reaction pathway by calculating the transition state energies of the possibly generated intermediates of this rearrangement, and concluded the intermediary formation of the corresponding ketene resulting from the [1,5]-H shift of the aldehyde. However, they did not succeed in the intermolecular capture of the intermediate **3** with some alcohols, presumably because their compounds would further proceed the intramolecular cascade reactions under the microwave irradiation conditions at high temperature (> 160 °C). Meanwhile, our compound, such as **13** possessing an ester group at the C3 position, would be favorable for the pericyclic reaction as already reported,[9] and that led to the formation of the versatile ketene, which could react with various alcohols and olefins.

We then further examined the substituent effect at the C3 position (Scheme 5). Under the established condition, dienal with 3-t-butyldiphenylsiloxymethyl instead of 3-ethoxycarbonyl derivative **36** gave trace of the rearranged product **36p**, and 74% of the starting materials **36** and **36′** (2.7:1 of E/Z isomers at C2) were recovered after 3 h (compared to Entry 1 in Table 2). After 24 h, the rearranged product **36p** was obtained in 25% yield along with the starting material of 51% (1:1 of E/Z isomers at C2). In the case of cis-β-ionylideneacetoaldehyde (**37**), though simple distillation in vacuo of this dienal was reported to give a [2 + 2] cycloaddition product via the [1,5]-H shift of the aldehyde hydrogen (Scheme 1B),[7] **37** was completely recovered under the established condition (compared to Entry 8 in Table 2). These results clearly indicated that the ester group at the C3 position remarkably accelerated the rearrangement.

Scheme 5. Substituent Effect at C3 Position
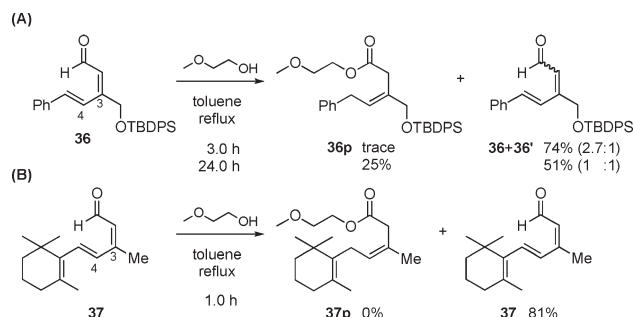
In conclusion, we have clearly demonstrated that the thermal [1,5]-H shift of the aldehyde hydrogen in linear dienal compounds is a feasible reaction to produce the corresponding ketene under a relatively mild condition, which was followed by capturing the intermediary-produced ketene with both an alcohol and olefins yielding the corresponding ester and [2 + 2] cycloadducts. Applications of this novel ketene formation to the synthesis of biologically active natural products as well as its mechanistic study are currently underway in our laboratory.

Supporting Information Available. The experimental details of reactions and ^{1}H and ^{13}C NMR spectra of the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.