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Communication

Cyclopropane Reactivity

Unexpected Vinylcyclopropane Rearrangement: New Strategies toward Skipped Dienes Using Sulfonium Ylides

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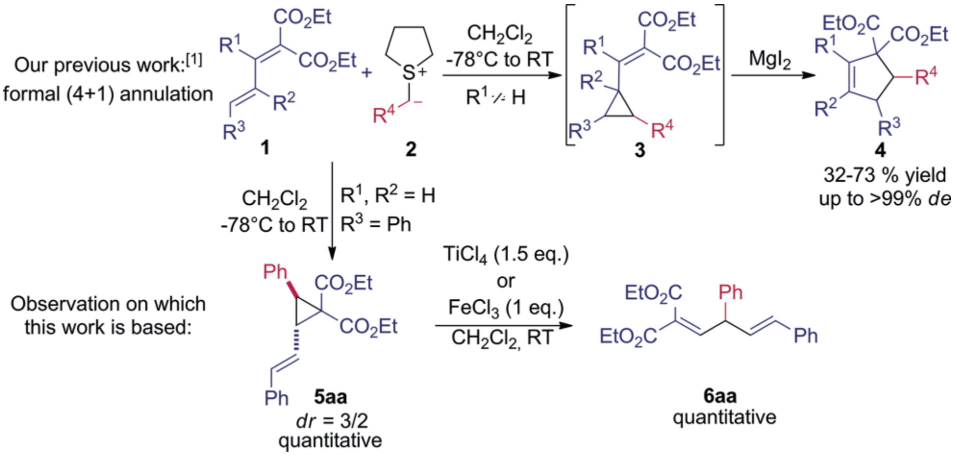
This manuscript is dedicated to Jeremy N. Harvey on the occasion of his 50th birthday.

Abstract: Vinylcyclopropanes are key intermediates in organic chemistry which undergo several important rearrangements. Herein, we report on an unexpected rearrangement of vinylcyclopropane into skipped diene proceeding at room temperature and with high selectivity. Deuteration experiments indicate that the mechanism of this rearrangement involves regioselective ring-opening of the cyclopropane ring followed by 1,2-migration of an aryl group. Based on this transformation, two complementary strategies toward skipped dienes bearing an aryl group on the central center were developed using sulfonium ylides.

Introduction

Vinylcyclopropanes are powerful and versatile intermediates in organic chemistry which find numerous applications in the synthesis of complexes molecular architectures as they are readily accessible and the basis of numerous methodologies.[1] Indeed, they easily undergo ring-opening reactions (releasing ring strain) to generate reactive species that can be used in a range of important reactions such as (3+2)[2] or (5+2)[3] cycloadditions or rearrangement into a cyclopentene.[4]

We recently made use of this special reactivity of vinylcyclopropanes to develop a (4+1) annulation strategy toward cyclopentenes from sulfur ylides and 1,3-dienes (Scheme 1).[5] In this context, we observed that when the 1,3-diene **1** is not substituted in position 2 and 3 (R^1, R^2 = H), a regioselective 1,4-addition –and not 1,6-addition – of the sulfonium ylide **2** is occurring, leading to vinylcyclopropane **5aa**. This latter, unlike **3**, was found to be unreactive upon MgI_2 catalysis. We now have attempted other reaction conditions to rearrange **5aa** and, interestingly, found that it leads quantitatively to skipped diene **6aa** in the presence of $TiCl_4$ or $FeCl_3$.[6]



Scheme 1. Previously developed formal (4+1) annulation strategy[5] and our observation when R^1, R^2 = H.

Herein, we report the study of this unexpected rearrangement of vinylcyclopropane and its application to the develop-

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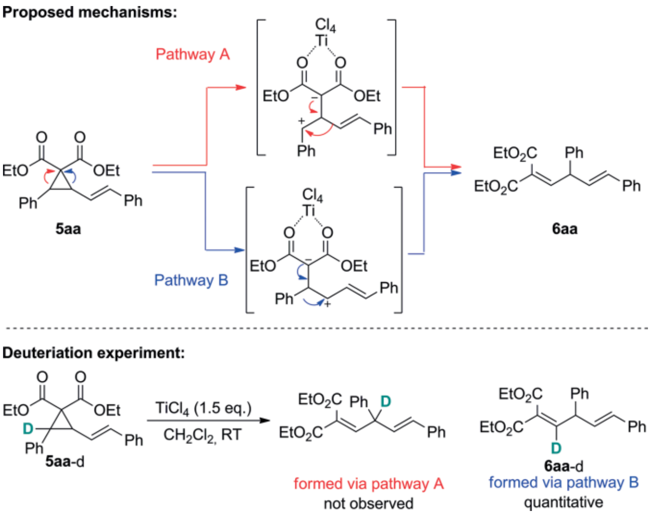
ment of two complementary strategies toward skipped dienes bearing a central stereogenic centre.

Results and Discussion

We first sought to decipher the mechanism of the observed rearrangement of vinylcyclopropane **5aa** into skipped diene **6aa**. We reasoned that this rearrangement could involve the ring-opening of the three-membered ring, to form a zwitterion,[7] followed by the 1,2-migration of the group in β position of the carbocation. There are however two possibilities: the ring-opening can occur either on the benzylic side with the 1,2-migration of the styryl group or instead on the styryl side with the phenyl group migrating (pathway A and B in Scheme 2, respectively).[8] In order to support this mechanistic pathway and determine which group migrates, we set up a deuteration experiment (see Scheme 2). Indeed, depending on the pathway which is followed, the deuterium atom initially at the benzylic position in the cyclopropane will end up in a different position in the skipped diene. The rearrangement of **5aa–d** led quantitatively to skipped diene **6aa–d**, thus indicating that the ring opens on the styryl side and that it is the phenyl group which migrates (pathway B in Scheme 2).



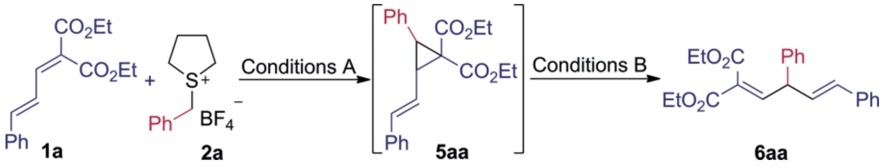
Scheme 2. Postulated mechanisms and deuteration experiment.

The mechanism of the rearrangement understood, we worked on the development of an efficient synthesis of skipped dienes from sulfonium ylides and 1,3-dienes. To do so, we searched for a one-pot procedure allowing to perform the two steps, cyclopropanation and rearrangement, in one synthetic step. Using **1a** and **2a** as model substrates, various one-pot conditions were explored (Table 1). These experiments showed that the base we used in our (4+1) annulation methodology (see Scheme 1), LiHMDS, is not compatible with a one-pot procedure (see entries 1–2). Indeed, only cyclopropane was observed in the crude mixture indicating that the rearrangement does not occur under these reaction conditions. A control experiment shows that addition of HMDS to the $TiCl_4$-catalyzed rearrangement prevents the reaction, probably due to its basicity. We then changed for NaH as a base and, in this case, skipped diene **6aa** was obtained in 90 % isolated yield using $TiCl_4$ (entry 3) whereas the rearrangement was still not working under iron-catalysis (entry 4).

With effective one-pot conditions in hand, the scope of the methodology was investigated (Table 2). First, a range of 1,1-dicarbonyl ester 1,3-dienes with different substituent patterns[9] was explored. Halogen and ester substituted aryl groups were found to be compatible with the methodology, yet leading to lower yields (entries 2–4). Additional substitution on position 4 of the 1,3-diene moiety is tolerated as well (entry 9).

The substitution of the benzylic sulfonium ylide was also varied. The reaction works nicely with electron-donating and slightly electron-withdrawing substituents on the aromatic group (see entries 4–6 in Table 2). However, in line with generally observed migratory aptitude in pinacol[10] and Wagner–Meerwein[11] rearrangements, electron-poor aryl groups are found to migrate less efficiently than electron-rich ones (see entries 7–8). For R^1 = *p*-CO_2MePh, the vinylcyclopropane is even unreactive toward the rearrangement; vinylcyclopropane was observed in the crude mixture with no traces of skipped diene (entry 8).

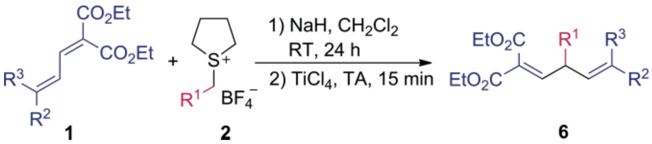
Table 1. Development of a one-pot procedure toward skipped dienes.



Entry	Conditions A	Conditions B	Yield [%][a]
1	LiHMDS (1.2 equiv.), –78 °C to r.t., 1 h	$TiCl_4$ (1 equiv.), r.t., 15 min	0 (91 % **5aa**)
2	LiHMDS (1.2 equiv.), –78 °C to r.t., 1 h	$FeCl_3$ (1 equiv.), r.t., 24 h	0 (73 % **5aa**)
3	NaH (1.6 equiv.), r.t., 24 h	$TiCl_4$ (1 equiv.), r.t., 15 min	90
4	NaH (1.6 equiv.), r.t., 24 h	$FeCl_3$ (1 equiv.), r.t., 24 h	0 (86 % **5aa**)

[a] Yields correspond to pure isolated material.

Table 2. Synthesis of skipped dienes from benzylic sulfonium ylides and 1,3-dienes.



Entry	R^2	R^3	R^1	Yield [%][a]
1	Ph	H	Ph	90
2	*p*-BrPh	H	*p*-FPh	19[b,c]
3	*p*-ClPh	H	Ph	26[c]
4	*p*-CO_2MePh	H	Ph	45
5	Ph	H	*p*-MeOPh	95
6	Ph	H	*p*-MePh	80
7	Ph	H	*p*-FPh	43[c,d]
8	Ph	H	*p*-CO_2MePh	0[d]
9	Me	Me	Ph	15

[a] Unless noted otherwise, yields correspond to isolated, analytically pure material. [b] TEMPO 10 mol-% were added and the reaction was performed in a dark room. [c] Yield determined on the crude mixture by ^1H NMR using an internal standard. [d] Vinylcyclopropane was observed in the crude mixture together with a complex mixture of unidentified products.

We envisioned that vinylcyclopropane intermediate **5** could also be obtained from an activated olefin **8**, instead of a 1,3-diene, if an allylic sulfonium ylide was used. Indeed, reaction of activated olefins **8** with a series of allylic sulfonium ylides (**9**) provides corresponding vinylcyclopropanes (Table 3). Rearrangement of these later under our optimized conditions ($TiCl_4$, r.t., 15 min) leads to corresponding skipped dienes in moderate to high yield.[12] In some the cases (entries 2 and 5), substoichiometric amount of $TiCl_4$ (0.4 equiv.) could be used without alteration of the yield. Again, the breadth of tolerated substituents was found to be broad. Migration of 2-furyl and styryl groups could even be observed (entries 14 and 6, respectively). However, our attempts to observe the migration of *p*-CO_2MePh group failed again (entry 8 and vide supra) as well as those with an alkyl group (entry 11).

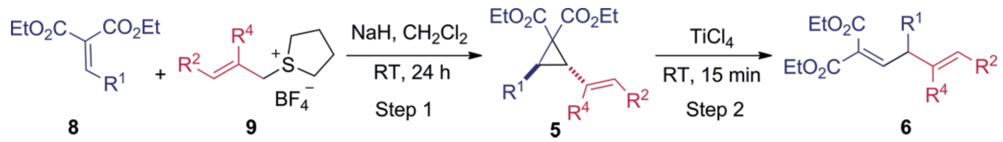
Conclusion

We have identified a new rearrangement of vinylcyclopropane into skipped dienes with a stereogenic centre at the central position. Conversely to previously reported rearrangements,[6] this rearrangement was found to be very selective and proceed at room temperature (15 min, r.t., $TiCl_4$ catalysis). Based on deuteration experiments we proposed a mechanism for this transformation which involves a regioselective ring-opening of the cyclopropane followed by a 1,2-migration of an aryl group. We exploited this rearrangement to develop two complementary strategies toward skipped dienes using sulfonium ylides. In both cases, a good functional group tolerance was demonstrated over a range of substrates. We are currently working on expanding further the scope of these methodologies as well as investigating factors which control reactivity and selectivity in this rearrangement.

Experimental Section

Typical Procedure for the Synthesis of Vinylcyclopropane (5): NaH (1.5 equiv.) is introduced into a dry round-bottom flask under argon atmosphere and washed three times with dry *n*-hexane. Then, dichloromethane (1 mL/20 mg of sulfonium salt) and olefin **8** (1 equiv.) are added. The sulfonium salt (**9**, 1.5 equiv.) is added whilst stirring at room temperature. After 24 h, water is added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1 M) and

Table 3. Synthesis of skipped dienes from allylic sulfonium ylides and activated olefins.



Entry	R^1	R^2	R^4	Yield [%][a] Step 1[b]	Step 2
1	Ph	Ph	H	90	95
2	*p*-MeOPh	Ph	H	61	Quant.
3	*p*-FPh	Ph	H	67	71
4	*p*-CO_2Me	Ph	H	53	0[d]
5	Ph	Ph	Me	19	54
6	CH=CHPh	Ph	H	32	(80)[c]
7	Ph	*p*-CO_2MePh	H	55	Quant.
8	Ph	*p*-MePh	H	32 (80)[c]	40
9	*p*-MePh	Ph	H	42	95
10	Ph	*i*Pr	H	97	15 (90)[c]
11	*i*Pr	Ph	H	86	0[d]
12	Ph	Ph	H	90	95
13	Ph	H	H	11 (90)[c]	(41)[c]
14	2-furyl	Ph	H	95	Quant.

[a] Unless noted otherwise, yields correspond to pure isolated material. [b] *Cis/trans* diastereoselectivity ranges from 1:1 to 3:7 as measured by ^1H NMR on the crude mixture. [c] Yields in parentheses correspond to crude yields determined by H^1 NMR using an internal standard (see the Supporting Information for details). [d] Exclusive formation of corresponding cyclopentene (see Supporting Information).

brine. The organic layer is dried with $MgSO_4$ and concentrated under reduced pressure. The vinylcyclopropane (**5**) is then purified by flash column chromatography.

Typical Procedure for the Synthesis of Skipped Dienes (6) from Vinylcyclopropanes (5): Vinylcyclopropane (**5**, 1 equiv.) and dry dichloromethane (1 mL/10 mg of **5**) were introduced in a round-bottom flask under argon atmosphere. Titanium tetrachloride 1 M in dichloromethane (1 equiv.) is added and the mixture is stirred at room temperature for 15 min. Water is then added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1 M) and brine. The organic layer is dried with $MgSO_4$ and concentrated under reduced pressure. The skipped diene (**6**) is then purified by flash column chromatography.

Typical Procedure for the One-pot Synthesis of Skipped Dienes (6) from Activated 1,3-Dienes (1): NaH (1.5 equiv.) is introduced into a round-bottom flask under argon atmosphere and washed three times with dry *n*-hexane. Dichloromethane (8 mL/100 mg of **1**) and the 1,3-diene (**1**, 1 equiv.) are then added. The sulfonium salt (**2**, 1.5 equiv.) is added whilst stirring at room temperature. After 24 h, a solution of $TiCl_4$ (1 equiv., 1 M in dichloromethane) is added. The reaction mixture is stirred for 15 min at room temperature. Water is then added to stop the reaction. The two layers are separated and the organic one is washed with an aqueous solution of hydrochloric acid (1 M) and brine. The organic layer is dried with $MgSO_4$ and concentrated under reduced pressure. The skipped diene (**6**) is then purified by flash column chromatography.

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