Highly Functionalized 4-Alkylidenebicyclo[3.1.0]hex-2-enes by Tandem Michael Addition and Annulation of Electron-Deficient Enynes

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Domino reactions are of high importance in synthetic chemistry, since they can combine several transformations into one-step and thus provide a rapid access to architecturally complex molecules from relatively simple starting materials.^[1] Recently, tandem reactions consisting of ylide routes leading to fused bicyclic compounds have attracted the interest of many chemists.^[2,3] In the context of our ongoing efforts to develop novel chemistry of electron-deficient enynes,^[4] we report herein a novel selective tandem Michael addition and annulation of a crotonate-derived sulfur ylide with electron-deficient enynes for the rapid construction of highly functionalized 4-alkylidenebicyclo[3.1.0]hex-2-enes.^[5]

Very recently, a tandem reaction of crotonate-derived sulfonium salt **1** with α , β -unsaturated ketones for synthesis of cyclohexadiene epoxides in high efficiency was reported by Tang (see Scheme 1).^[2a] We have just reported that the reactions of conjugated yne-enone **3** with ylide **2** proceeded smoothly to produce the cyclopropane derivatives via the cyclopropanation reaction of the C=C double bond. The cycloadducts can be further converted into fused bicyclic furans under the catalysis of a Rh^I species under a CO atmosphere.^[6] To our surprise, we found that the reaction of conjugated eny-enone **3a** with sulfonium salt **1** gave the novel bicyclo[3.1.0]hex-2-ene **4a** rather than cyclopropanes and cyclohexadiene epoxides in the presence of base. The reaction is complete in 0.5 h at 0°C in EtOH using 4 equiva-

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Scheme 1. Previous work on ylide reaction of 1 and 2.

lents of Et_3N to furnish the desired product **4a** with a 72% yield of isolated product and a trace amount of unidentified product (Table 1, entry 1). The structure of **4a** was further

Table 1. Screening the reaction conditions of tandem cyclization of **3a** with sulfonium salt **1**.

	Ph O	$(H_3C)_2S$ 1		Ph		
	Ph	Base, So	vent : "Ph CO-Me			
	3a			4a		
Entry ^[a]	Base [equiv]	Solvent	Time [h]	Isolated yield [%]		
1	Et ₃ N (4.0)	EtOH	0.5	72		
2	Et ₃ N (2.4)	EtOH	2	58		
3	Et ₃ N (3.0)	EtOH	1.5	69		
4	Na_2CO_3 (4.0)	EtOH	4	64		
5	$Et_{3}N$ (4.0)	MeOH	0.5	66		
		CH ₃ CN	0.8	54		
		DCM	3.5	59		
		DCE	7	64		
		THF	3.5	65		
		toluene	25	55 ^[c,d]		
		DMF	0.5	60 ^[c]		
		EtOH	0.5	48 ^[c]		
13	Li_2CO_3 (4.0)	THF	30	trace ^[d]		
14	Cs_2CO_3 (4.0)	THF	10	57		
15	DBU (4.0)	THF	3	50 ^[c]		
16	$Et_{3}N(4.0)$	THF	26	58 ^[c]		

[a] Unless otherwise noted, all reactions were carried out at 0°C in 0.3 mmol scale. [b] Isolated yield. [c] Yield measured by ¹H NMR, with CH_2Br_2 as an internal standard. [d] The reactions were carried out at RT.

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confirmed by single crystal X-ray diffraction (Figure 1).^[7] Reducing the equivalents of Et₃N resulted in decreasing slightly the yield (entries 2–3). Further studies showed other



Figure 1. ORTEP representation of **4a**.

bases such as Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , and DBU are slightly less effective. However, Li_2CO_3 is ineffective to mediate this reaction even at elevated temperature. Solvents also have effects on the reaction. For example, the reaction run in THF gave the product **4a** in a relatively lower yield (58%, entry 16) than the one in EtOH (72% yield).

With the optimal reaction conditions in hand, we next study the scope of conjugated yne-enone 3 and the results are summarized in Table 2. These results showed that all three substitutents (R¹⁻³) could be not only aryl but also aliphalic to afford the corresponding bicyclo[3.1.0]hex-2-ene derivatives in moderate to good yields (entries 1-13). Introduction of an electron-donating group to the aryl ring of R^1 decreased the reactivity and the reaction furnished the desired product in relatively lower yield. For example, the reaction of **3f** was complete after 12 h to give **4f** in 62% yield, whereas the reaction of **3g** furnished **4g** in 85% yield after 0.5 h (entries 5 and 6). It is interesting that the reaction of (E)-methyl 3-benzylidene-2-oxo-5-phenylpent-4-ynoate (3j) also gave the corresponding 4-alkylidenebicyclo-[3.1.0]hex-2-ene 4j in 47% yield. The yne-enone 3l is not stable under the reaction conditions and gives the desired product in 30% yield (entry 11). It is also noteworthy that all these reactions give the cycloadducts as a single diastereomer, indicating that this tandem transformation is highly selective.

Table 2. Synthesis of multi-functionalized bicyclo[3.1.0]hex-2-ene derivatives.



[a] Unless othewise noted, all reactions were carried out using **3** (0.3 mmol), **1** (0.6 mmol), Et_3N (1.2 mmol), EtOH (3 mL) at 0 °C and yield is yield of isolated product. [b] K_2CO_3 and THF were used.

The generality of this transformation was also investigated using the (E)-2-benzylidene-4-phenylbut-3-ynenitrile **5** and (E)-enyne **7** (Scheme 2). To our delight, the reaction of **5**



Scheme 2. The tandem reactions of 5 and 7 with 1.

could give the desired bicyclic product **6** in a yield of isolated product of 73 % after stirring the reaction for 9 h at RT. The reaction of **7** can also give a moderate yield of bicyclic cycloadduct **8**. In this case, K_2CO_3 is a better base than Et_3N and gives a slightly better yield, however, the reason for this increase is not clear.

The preliminary result [Eq. (1)] showed that the camphorderived sulfonium salt $9^{[2a]}$ could react with yne-enone **3a** to give **4a** in a yield of isolated product of 69% with 38% *ee*. Although the *ee* value is only moderate, it is still a good example for controlling three stereogenic centers including two all-carbon quaternary ones in a single operation.



A plausible mechanism for this novel tandem transformation is depicted in Scheme 3. The crotonate-derived sulfonium salt $\mathbf{1}$ was treated with Et₃N to give an allylic ylide with



Scheme 3. A proposed mechanism for this domino process.

two resonance structures **A** and **B**, which undergo a Michael addition with **3a** to produce a new ylide $C.^{[2a]}$ The subsequent stereoselective intramolecular Michael addition of **C** from the side opposite the phenyl group gave the intermediate **D**, which would in turn undergo a stereoselective intramolecular SN2' nucleophilic substitution to furnish the product **4a**. The two newly formed stereogenic centers are effectively induced by the adjacent phenyl group.

In summary, we have developed a novel tandem Michael addition and ylide annulation of a crotonate-derived sulfur ylide with readily available electron-deficient enynes, which provide a rapid, efficient, and selective route to multi-functionalized 4-alkylidenebicyclo[3.1.0]hex-2-enes. It is note-worthy that not only the stereochemistry of all three newly formed carbon stereogenic centers, including two all carbon quaternary ones, but also the double bond could be controlled in this domino process. Further studies on the synthesis of other chiral sulfur ylides and their applications in this transformation are ongoing in this laboratory.

Experimental Section

Typical procedure for the synthesis of 4a (Table 1, entry 1): To a stirred mixture of sulfonium salt 1 (145 mg, 0.6 mmol) and 3a (93 mg, 0.3 mmol) in EtOH (3 mL), Et₃N (122 mg, 1.2 mmol) was added, and the resulting solution was stirred at 0°C until the reaction was complete (monitored by TLC). Then the reaction mixture was diluted with water (3 mL), and extracted with CH₂Cl₂. The organic layers were combined, washed with brine (10 mL), and dried over anhydrous MgSO₄. After filtration and concentration under reduced pressure, the crude product was purified by flash column chromatography on silica gel (hexanes/AcOEt=30:1) to afford 88 mg (72%) of 4a as a white solid. M.p.: 134-136°C (hexanes/ CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): $\delta = 7.34-7.16$ (m, 13 H), 7.10 (t, J=7.5 Hz, 2H), 6.50 (s, 1H), 6.36 (d, J=5.4 Hz, 1H), 6.05 (d, J=5.4 Hz, 1H), 4.55 (s, 1H), 3.58 ppm (s, 3H); 13 C NMR (75.4 MHz, CDCl₃) δ 194.11, 168.98, 142.69, 136.26, 135.46, 135.41, 133.44, 132.09, 130.28, 129.98, 128.45, 128.99, 128.05, 128.00, 127.71, 127.59, 127.48, 126.97, 54.62, 53.78, 52.45, 42.95 ppm; MS (EI) m/z (%): 406 [M⁺] (12.76); HRMS calcd for C₂₈H₂₂O₃: 406.1569, found: 406.1564. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

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