ORGANIC LETTERS
2005
Vol. 7, No. 18
4057−4059

Highly Diastereoselective Formation of 1,2,3-Trisubstituted Cyclopropane Derivatives

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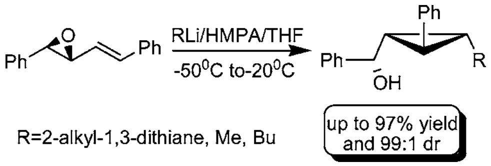
Received July 14, 2005

ABSTRACT



A highly diastereoselective formation of cyclopropane derivatives was reported. When the chiral phenylvinyl epoxide reacted with lithiated 2-alkyl-1,3-dithiane or lithiated alkyl carbonanion in the presence of HMPA, cyclopropanes bearing stereochemistry at all three positions on the ring were readily obtained in high yields of 80–97% and high dr values of 68:32–99:1. This reaction was supposed to be a tandem conjugation addition–epoxide opening sequence.

Domino reactions have become very powerful synthetic tools in organic synthesis. They not only reduce the production of waste and the consumption of solvents; they also create several bonds in one sequence without the isolation of intermediates. Importantly, if cyclizations are involved in this sequence, in most cases, ring closure proceeds in a highly stereoselective fashion. This makes domino reactions highly attractive for natural product synthesis and related applications.[1] Michael-induced ring-closing (MIRC) reactions play an important role in this field of chemistry, and many synthetic applications have been described in the literature so far.[2]

In this reaction, olefins that behave as the Michael acceptor must be activated by one or two strong electron-withdrawing groups. There were few literature examples using unactivated cinnamate derivatives as Michael acceptors in MIRC reactions, and they were only used to synthesize 1,2-disubstituted cyclopropanes.[3] Herein, we report a new approach to synthesize 1,2,3-trisubstituted cyclopropanes with high diastereoselectivity using unactivated phenylvinyl epoxides as the Michael acceptors.

Initially, we attempted to study the S_N2' reaction of the racemic phenylvinyl epoxide **1a** under the reaction conditions reported by A. B. Smith, III.[4] Lithiated 2-ethyl-1,3-dithiane **2a** was first examined as a nucleophile. In the presence of HMPA, the reaction of **2a** with **1a** proceeded smoothly at −50 to −20 °C in anhydrous THF. However, to our surprise,

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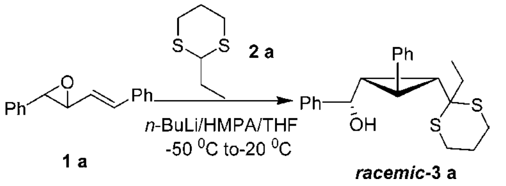
10.1021/ol051653t CCC: $30.25

Scheme 1. Cyclopropanation of Phenyl Vinyl Epoxide with Lithiated 2-Ethyl-1,3-dithiane



we did not obtain the expected product of S_N2 or S_N2' reaction. Instead, a single product was obtained in high yield, which was identified as 1,2,3-trisubstituted cyclopropane **3a** by NMR and X-ray analysis (Scheme 1).[5] Further studies showed that HMPA[6] and low reaction temperature were critical for this reaction to proceed. In the absence of HMPA, no reaction took place, and the starting material **1a** was completely recovered. When the reaction was warmed to room temperature, the reaction mixture became complex, and it was difficult to separate the desired product **3a**. Moreover, the solvent played an important role in this reaction. For example, the use of anhydrous THF as the solvent led to the formation of **3a** in high yield, whereas in toluene and ethyl ether the reaction did not proceed satisfactorily. Several other racemic vinyl epoxides[7] were applied under the same conditions to demonstrate the utility of this cyclopropanation reaction, and the results are summarized in Table 1. When monoepoxides of diaryl-substituted dienes were examined (Table 1, entries 1−5), 1,2,3-trisubstituted cyclopropanes were obtained as the single products in high yields. When the aryl group on the epoxide ring was replaced by an alkyl group such as *n*-butyl (Table 1, entry 6), the reaction was complex, and the desired cyclopropane product was obtained only in a minor amount. Consistent with Smith's result,[4] when vinyl epoxide was used as the substrate (Table 1, entry 7), a mixture of S_N2 and S_N2' products was obtained in 80% yield. Therefore, it is crucial to have an aryl group on the termination of the olefins and an aryl group on the termination of the epoxide for this cyclopropanation reaction to occur under the current reaction conditions.

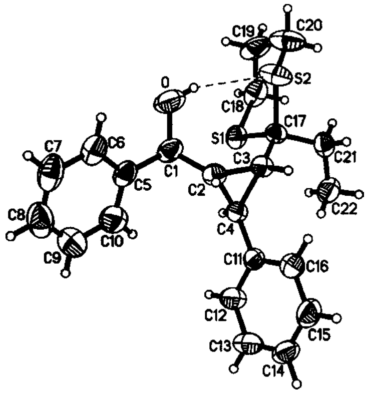
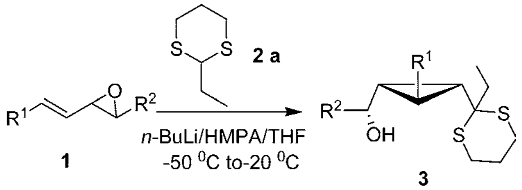


Figure 1. X-ray structure of **3a** (CCDC deposition no. 222201).

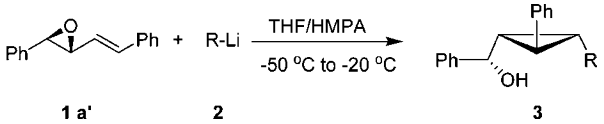
Table 1. Cyclopropanation of Substituted Phenyl Vinyl Epoxide with Lithiated 2-Ethyl-1,3-dithiane



entry[a]	1	R¹	R²	3	yield[b]
1	**1a**	Ph	Ph	**3a**	90
2	**1b**	4-Cl−Ph	Ph	**3b**	95
3	**1c**	Ph	4-Cl−Ph	**3c**	88
4	**1d**	4-Cl−Ph	4-Cl−Ph	**3d**	91
5	**1e**	Ph	4-CH_3−Ph	**3e**	80
6	**1f**	Ph	Bu		
7[c]	**1g**	H	Ph		

[a] Reaction conditions: 1 mmol of substrate (**1**), 2 mmol of lithiated carbon anions (**2a**), 3 mmol of HMPA, 10 mL of anhydrous THF, −50 to −20 °C, 20 h. See Supporting Information for details. [b] Isolated yield. [c] Mixture of S_N2 and S_N2' products were obtained in ratio of 1:4 in a total yield of 80%.

Table 2. Cyclopropanation of Chial Phenyl Vinyl Epoxide with RLi



entry[a]	R	3	yield (%)[b]	dr[c]
1	2-ethyl-1,3-dithianyl	**3a′**	97	98:2
2	2-methyl-1,3-dithianyl	**3f**	95	99:1
3	1,3-dithianyl	**3g**	90	95:5
4	2-(*n*-propanyl)-1,3-dithianyl	**3h**	92	95:5
5	2-(*i*-propanyl)-1,3-dithianyl	**3i**	92	99:1
6	2-(*n*-butyl)-1,3-dithianyl	**3j**	96	99:1
7	2-(*i*-butyl)-1,3-dithianyl	**3k**	93	98:2
8	2-(1-propenyl)-1,3-dithianyl	**3l**	89	97:3
9	2-(3-methyl-1-propenyl)-1,3-dithianyl	**3m**	91	85:15
10	Me	**3n**	90	68:32
11	*n*-Bu	**3o**	95	95:5

[a] Reaction conditions: 1 mmol of substrate (**1**), 2 mmol of lithiated carbonanions (**2**), 3 mmol of HMPA, 10 mL of anhydrous THF, −50 to −20 °C, 20 h. See Supporting Information for details. [b] Isolated yield. [c] Dr values were determined by HPLC (see Supporting Information).

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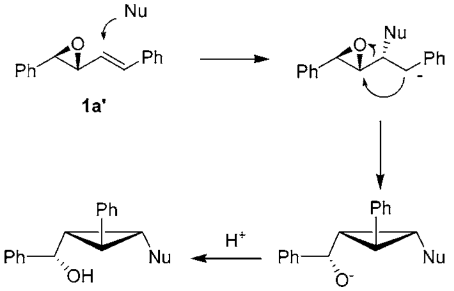
(5) Crystal data for **3a**: $C_{22}H_{26}OS_2$, $M_r = 370.55$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 6.604(1)$ Å, $b = 15.346(2)$ Å, $c = 19.811(3)$ Å, $\beta = 90\ (1)°$, $V = 2007.7(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.226$ g/cm^3, $\mu = 0.272$ mm^{-1}, $F(000) = 792$, $1.68 \leq 2\theta \leq 27.23°$, $-8 \leq h \leq 8$, $-19 \leq k \leq 19$, $-25 \leq l \leq 25$, 5561 data collected, 4493 unique data (R_{int}= 0.0144), 3302 data with $I > 2\sigma(I)$, 232 refined parameters, GOF($F2$) = 0.885, $R_1 = 0.0530$, w$R_2 = 0.0788$. The X-ray crystallographic structure of **3c** is shown in Figure 1. The crystallographic data have been deposited at the Cambrigde Crystallographic Data Center as supplementary publication No. CCDC 222201.

To further investigate the stereoselectivity of this cyclopropanation reaction, optically pure epoxide **1a′** was chosen as the model Michael acceptor; it was prepared from (*trans*,*trans*)-1, 4-diphenyl-1, 3-butadiene by Shi's method.[8] A variety of 1,3-dithianyllithiums were used to react with compound **1a′**, and the results are summarized in Table 2 (entries 1−9). The corresponding cyclopropanation products **3** were obtained in high yield (89−97%) and high diastereoselectivity (85:15−99:1). More interestingly, under the same reaction conditions, alkyllithium reagents also proved to be good nucleophiles, converting compound **1a′** into the corresponding cyclopropane derivatives in 90−95% yield (Table 2, entries 10 and 11). For *n*-butyllithium, the diastereoselective ratio of the cyclopropane product **3o** was as high as 95:5, whereas methyllithium gave product **3n** in a 68:32 diastereomeric ratio.

On the basis of the experimental results, an MIRC mechanism is suggested (Scheme 2). This cyclopropanation reaction probably involves a tandem conjugation addition−epoxide-opening sequence.

In summary, we have developed a new and highly diastereoselective process for the synthesis of 1,2,3-trisubstituted cyclopropane derivatives in high yields. Using this strategy, cyclopropane derivatives bearing stereochemistry at all three positions on the ring can be easily synthesized. Investigation of the mechanism and further application of this reaction in synthesis are underway.

Scheme 2. Supposed Mechanism



Acknowledgment. We are grateful for the generous financial support by the Special Doctorial Program Funds of the Ministry of Education of China (20040730008), A Hundred Talents Program of CAS, NSFC (QT program, No.20372026) and the key grant project of Chinese ministry of Education(No.105169).

Supporting Information Available: Typical experimental details and characterization data for all new compounds, as well as crystal data of **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Racemic vinyl expoxides were easily obtained in high yield starting from the corresponding allyl alcohols via *m*-CPBA epoxidation, Swern oxidation, and wittig olfination sequences; see Supporting Information for details.

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