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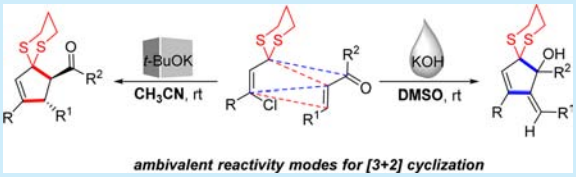
Direct Regioselective [3 + 2]-Cyclization Reactions of Ambivalent Electrophilic/Nucleophilic β-Chlorovinyl Dithianes: Access to Cyclopentene Derivatives

Yongping Liang,[†] Junshan Lai,[†] Teng Liu,[†] and Shouchu Tang*[,†,‡]

[†]School of Pharmacy and [‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

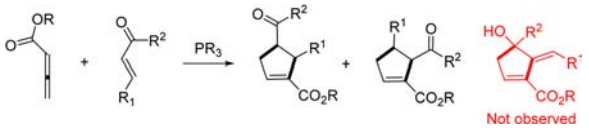
Supporting Information

ABSTRACT: The highly regioselective and operationally straightforward [3 + 2] cyclizations of β-chlorovinyl dithianes with α,β-unsaturated carbonyl compounds have been developed. This protocol provides direct access to highly functionalized cyclopentenes with perfect chemo- and regioselectivities under extremely mild reaction conditions. In particular, the unprecedented cyclization allows for the selective preparation of hydroxylated cyclopentenes.



Substituted cyclopentenes and structurally related cyclopentenones serve as key structural components in numerous medicinally important compounds and biologically active molecules.[1,2] As a result, extensive development of various strategies has been employed toward their preparation.[3,4] Occurring as stepwise or concerted processes, [3 + 2]-cycloaddition represents a particularly useful and direct approach to prepare these five-membered carbon rings. The most frequently applied method involves organic base-catalyzed [3 + 2] cycloaddition of allenoates and enones (Scheme 1).[5]

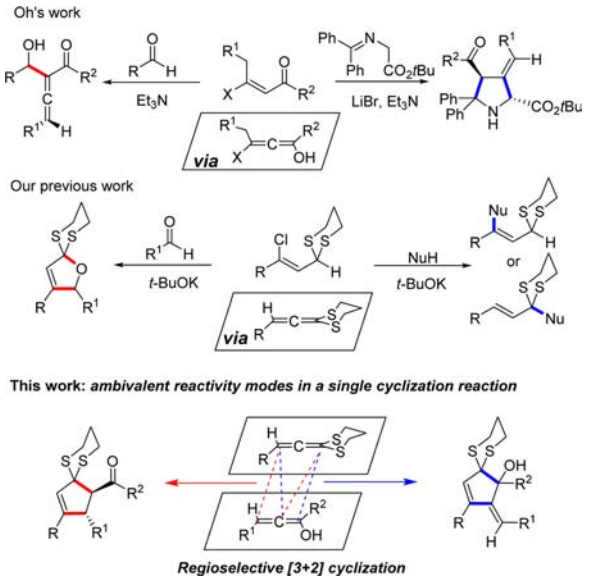
Scheme 1. Formal [3 + 2] Cycloaddition of Allenoates and Enones



These reactions are versatile, but mixtures of isomers are often formed in most cases, and the [3 + 2] cyclization protocols can only be of practical synthetic utility if one can control the regioselectivity issues. Modifications of both substrates and cyclization conditions have led to several versatile and efficient protocols for the selective preparation of compounds containing carbocycles.[6] Nevertheless, methods for direct formation of hydroxylated cyclopentenes are limited. Furthermore, the search for new strategies that offer regioselective methodology for the synthesis of a substantial variety of cyclopententenes remains a topic of considerable interest.

In general, α,β-unsaturated carbonyl compounds constitute one of the most frequently used electrophiles that readily accommodate an appropriate nucleophile.[7] Nevertheless, alternative synthetic methods have been developed for the successful formation of allenol/allenolates or vinyl carbanions from α,β-unsaturated compounds.[8] In terms of the reactivity modes, these studies allow the ambivalent reactivity of α,β-unsaturated carbonyl compounds toward electrophiles as well as nucleophiles with controlled stereoselectivity (Scheme 2).

Scheme 2. Nucleophilic and Electrophilic Reactivity Modes of β-Chlorovinyl Ketone and β-Chlorovinyl Dithiane



More recently, Oh and co-workers have disclosed the nucleophilic and electrophilic reactivity modes of β-chlorovinyl ketones in the development of novel C−C bond forming reactions.[9] It revealed a soft vinyl enolization strategy of β-chlorovinyl ketones in which oxy-substituted [3]cumulene derivatives as nucleophilic species reacted with a protic source[9a] or aldehydes,[9b] and the ambivalent electrophilic reactivity mode

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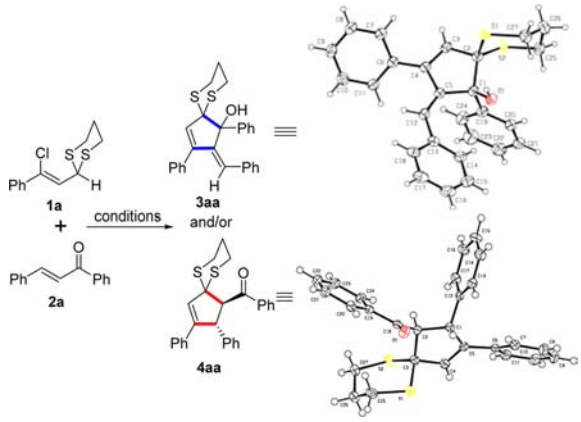
with ketimine esters via a formal [3 + 2] cycloaddition pathway.[9c]

Among various types of organic reagents, dithiane compounds serve as valuable umpolung intermediates in the field of synthetic organic chemistry because of their unique properties and reactivities.[10−12] Recently, the demonstrated ambivalent donor−acceptor (D−A) reactivities of β-chlorovinyl dithianes in our group have opened up a novel class of reaction pathways beyond the typical dithiane methods.[13] The development of [3 + 2]-cycloaddition has been achieved through identification of reactive vinylidene dithiane species and aldehydes.[13b] Our observation revealed that nucleophilic and electrophilic vinylidene dithiane intermediates can be generated from a variety of β-chlorovinyl dithianes under weakly basic conditions.

As a consequence of these observations, we therefore envisioned that the union of a chlorovinyl dithiane and an α,β-unsaturated carbonyl compound will greatly expand the [3 + 2] cyclization scope and introduce a new regioselective strategy that allows the direct construction of a highly functionalized cyclopentene in only one step. However, such ambivalent electrophilic and nucleophilic reactivity modes for the regioselective two-component cyclization are uncommon. Herein, we report our discovery of a highly regioselective, operationally simple cyclization protocol that successfully leads to highly functionalized cyclopentenes under extremely mild reaction conditions. Remarkably, our design demonstrates the first examples of the regioselective cyclization reaction of vinylidene dithiane and enone species that displayed both ambivalent electrophilic and nucleophilic reactivity modes. Such a process would install a tertiary and secondary alcohols with high chemselectivity and regioselectivity.

Our investigations commenced with the cyclization of equimolar amounts of β-chlorovinyl dithiane **1a** and chalcone **2a** under the previously reported conditions.[13] As shown in Table 1, we found promising results when employing an excess amount of base (3.0 equiv *t*-BuOK in DMSO). Unexpectedly, complete conversion was observed, and only the hydroxylated cyclopentene **3aa** was observed for a majority of product (entry 1). We next evaluated a series of Lewis acids,[14] such as $ZnCl_2$, $BF_3{\cdot}Et_2O$, and $FeCl_3$, but they all did not significantly influence reaction outcome and regioselectivities (entries 2−4). Interestingly, we further found that the treatment of aqueous base (5 M aq KOH)[15] in a DMSO solution was slightly beneficial and gave improved yields for the formation of the desired cyclopentene **3aa**, maintaining a good chemselectivity (entry 6). When a weak base such as Et_3N or Cs_2CO_3 was used at room temperature, no desired product was obtained (entries 7 and 8). Surprisingly, the solvent effect was found to directly influence the selectivities of the cycloadducts.[16] Gratifyingly, changing the solvent from DMSO to CH_3CN represented the key to achieving high chemselectivity and did not produce any observable amount of **3aa**, and we were pleased to see that a stoichiometric *t*-BuOK in CH_3CN provided the single regioisomer **4aa** in 82% yield with excellent dr value (dr >20:1) (entry 11). While the addition of Bronsted base such as Ph_3P did not facilitate the generation of **4aa** (entry 13),[5] the relative configuration of the cyclopentenes was analyzed by NMR spectroscopy, and the assignment of the structure *Z*-**3aa** and *trans*-**4aa** was supported by X-ray crystallographic analysis.[17] In addition, it is worth noting that access to such highly functionalized hydroxylated cyclopentene derivatives **3aa** is not readily accessible by other traditional nucleophilic means.[10]

Table 1. Optimization of the [3 + 2] Cyclization Reaction between 1a and 2a[a]



entry	solvent	base (equiv)	additives	yield,[b] (%) (**3aa**/**4aa**)
1	DMSO	*t*-BuOK (3.0)		58/nd[c]
2	DMSO	*t*-BuOK (3.0)	$ZnCl_2$ (10 mol %)	60/8
3	DMSO	*t*-BuOK (3.0)	$BF_3{\cdot}Et_2O$ (10 mol %)	57/trace
4	DMSO	*t*-BuOK (3.0)	$FeCl_3$ (10 mol %)	65/trace
5	DMSO	NaOH[d] (3.0)		56/trace
6	DMSO	KOH[d] (3.0)		69/trace
7	DMSO	Et_3N (3.0)		nr[e]
8	DMSO	Cs_2CO_3 (3.0)		nr
9	THF	*t*-BuOK (1.1)		20/35
10	toluene	*t*-BuOK (1.1)		25/40
11	CH_3CN	*t*-BuOK (1.1)		nd/82
12	CH_3CN	KOH (1.1)		nr
13	CH_3CN	*t*-BuOK (1.1)	Ph_3P (10 mol %)	nd/80

[a]Reaction conditions: **1a** (28.2 mg, 0.11 mmol, 1.1 equiv), **2a** (20.8 mg, 0.1 mmol, 1.0 equiv), and base (x equiv) dissolved in solvent (2 mL) at room temperature, 1 h. [b]Isolated yields. [c]No detected. [d]5 M aqueous solution. [e]No reaction.

Having established efficient conditions for regioselective cyclization, we set out to explore the substrate scope of this cyclization reaction for hydroxylated cyclopentenes **3**. We first examined the scope of β-chlorovinyl dithiane substrates for the selective cyclization (Table 2). A variety of β-chlorovinyl dithianes were tested, and the corresponding functionalized products **3ba−ga** were obtained under the optimized conditions that make use of aq KOH. Substrates with an electron-donating group, such as a methoxy and phenyl group, or an electron-withdrawing group, such as a chloro or a bromo group, at the para position of the benzene ring underwent the reaction smoothly to provide products with excellent regioselectivities. Next, the role of aryl substituent on α, β-unsaturated carbonyl compounds was probed to investigate the influence of electronic parameters on the transformation. All of them gave the corresponding cyclopentenes in good to excellent yields (entries 8−10). The electronic property of aryl groups has little influence on the product yields. Interestingly, reaction of an alkyl substrate such as benzal

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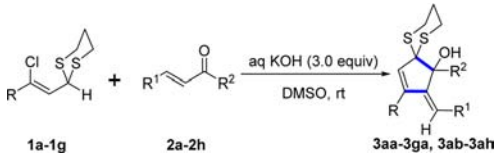
Table 2. Scope of the [3 + 2] Cyclization for Hydroxylated Cyclopentenes 3[a]



entry	R	R^1	R^2	product	yield,[b] (%)
1	Ph	Ph	Ph	**3aa**	69
2	4-MeC_6H_4	Ph	Ph	**3ba**	67
3	4-MeOC_6H_4	Ph	Ph	**3ca**	63
4	4-EtOC_6H_4	Ph	Ph	**3da**	72
5	biphenylyl	Ph	Ph	**3ea**	79
6	4-ClC_6H_4	Ph	Ph	**3fa**	80
7	4-BrC_6H_4	Ph	Ph	**3ga**	73
8	Ph	4-ClC_6H_4	4-ClC_6H_4	**3ab**	82
9	Ph	4-MeOC_6H_4	Ph	**3ac**	71
10	Ph	4-MeC_6H_4	4-ClC_6H_4	**3ad**	75
11	Ph	Ph	Me	**3af**	52
12	Ph	Ph	H	**3ag**	66
13	Ph	2-furyl	Ph	**3ah**	56

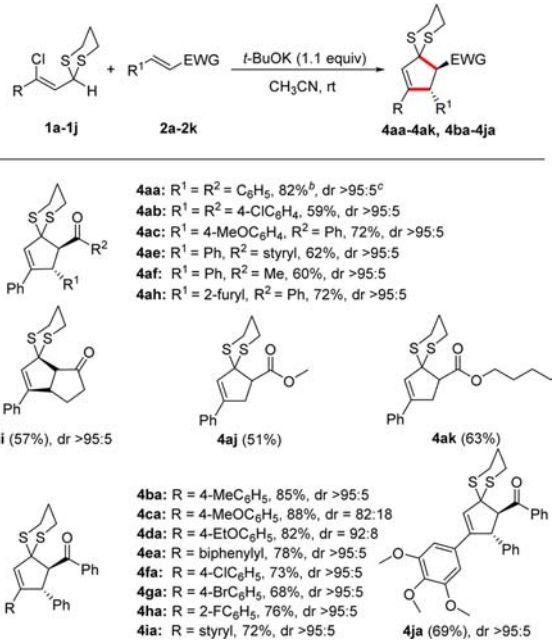
[a]Reaction conditions: **1** (0.25 mmol, 1.1 equiv), **2** (0.225 mmol, 1.0 equiv), 5 M KOH (aq, 3.0 equiv), DMSO (2 mL), room temperature, 30 min to 1 h. [b]Isolated yields.

acetone (entry 11) proceeded without any problems, whereas the reaction resulted in moderate yield (**3af**). Most importantly, treatment of cinnamaldehyde (entry 12) also gave the hydroxylated cyclopentene **3ag** in 66% yield with 21% of a substituted furan compound.[13b] Additionally, heteroaromatic enone was also applicable to this reaction (**3ah**).

As revealed in Scheme 3, a range of α,β-unsaturated carbonyls were subsequently examined for the selective formation of cyclopentenes **4** under our optimized conditions. These reactions preceded smoothly to give the desired cyclopentenes in good yields and with near-perfect regioselectivities in most cases. In general, full and clean reaction conversions were observed using CH_3CN as an optimal solvent within 1 h at ambient temperature without any isolable byproducts. Electron-rich and electron-deficient chalcone derivatives gave good yields of the corresponding cyclopentene products (**4aa**–**ah**). Notably, the reaction of cyclopentenone took place in 57% yield to give mainly a *syn*-cyclized product **4ai**. Methyl acrylate and butyl acrylate also efficiently underwent cyclization reactions and afforded the corresponding products **4aj** and **4ak**, respectively, in acceptable yields. For the subsitituted vinyl dithianes, both electron-rich and electron-poor groups were compatible with these reaction conditions, and no obvious substitution effect was observed (**4ba**–**ja**). Overall, all substrates gave clean conversion to cyclopentenes with high dr values, establishing that steric effects dominate the perfect regioselectivity for the cyclization reaction.

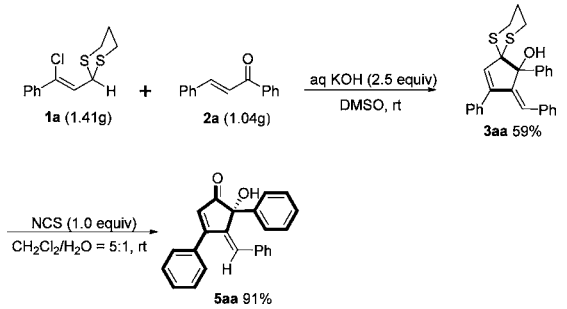
To evaluate the scalability of these cyclizations, the preparation of cyclopentene **3aa** has been performed on 5 mmol scales. Comparable to the small-scale procedure, hydroxylated cyclopentene **3aa** was accessed in 59% yield (Scheme 4). Most importantly, this method provides a potential strategy for the construction of hydroxylated cyclopentenone, an important structural motif that is found among biologically active natural products such as the antibiotic tylopilusins.[18] At this stage, the utility of this methodology was

Scheme 3. Substrate Scope of [3 + 2] Cyclization for Cyclopentenes 4[a]



[a]Reaction conditions: **1** (0.25 mmol, 1.1 equiv), **2** (0.225 mmol, 1.0 equiv), *t*-BuOK (1.1 equiv), CH_3CN (2 mL), room temperature, 1 h. [b]Isolated yields. [c]Determined by ^1H NMR spectroscopy.

Scheme 4. Gram-Scale and Synthesis of Hydroxylated Cyclopentenone 5aa



further realized by the synthesis of hydroxylated cyclopentenone **5aa** through a simple NCS-mediated desulfurization process.[19] However, the related desulfurization processe was unsuitable for the cyclopentene **4aa** to afford the corresponding 5-benzoylcyclopentenone compound.

To gain insight into the nature of the cyclization step, the radical scvenger TEMPO was added into the reactions of **1a** and **2a**. It was shown that the corresponding [3 + 2] cyclization reactions were not prohibited, and products **3aa** and **4aa** were obtained in good yields, indicating that the transformation might not proceed via a free-radical pathway. To further confirm the ambivalent electrophilic and nucleophilic behavior of β-chlorovinyl dithianes, we found **1a** underwent coupling reaction in 32% yield to give a mixture of regioisomers in a 5:1 ratio with high stereoselectivities,[20] resulting from the effect of steric properties of vinylidene dithiane on the regioselectivity of the vigronous process.

In summary, we have developed a regioselective protocol for the [3 + 2] cyclization of β-chlorovinyl dithianes with α,β-unsaturated carbonyl compounds under extremely mild

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reaction conditions that allow for the direct construction of highly functionalized cyclopentenes. This method features excellent chemselectivity and operational simplicity for efficient formation of carbocycles. Further investigations into the mechanistic details of these transformations, the asymmetric induction, and application in natural product synthesis are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02536.

Experimental details, characterization data for the products, NMR spectra (PDF)
Crystallographic data for **3aa** (CIF)
Crystallographic data for **4aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tangshch@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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