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Dithiane Induced Cycloaddition/Aromatization Tactic for the Synthesis of Multisubstituted Furans

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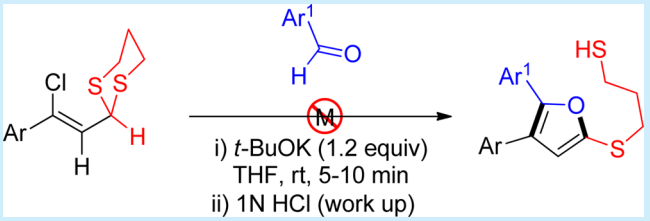
Supporting Information

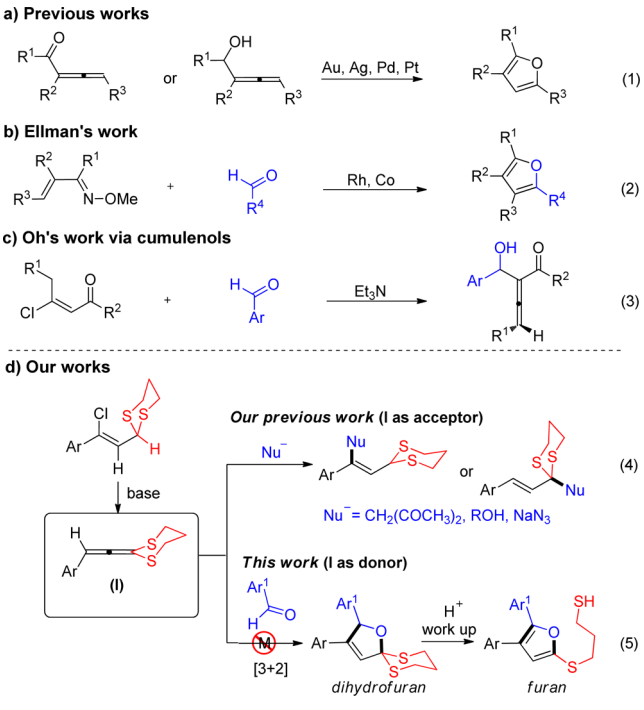
ABSTRACT: The development of a new transition-metal-free tactic for convergent, one-pot synthesis of multisubstituted furans by β-chloro-vinyl dithiane cyclization with aldehydes is described. Key to the success was the development of a new vinylidene dithiane site as a donor allene that generates the active dihydrofuran, which undergoes in situ aromatization under mild conditions.



Furans are common structural motifs in numerous biologically active molecules as well as in various pharmaceutically active compounds, functional materials, and agrochemicals.[1,2] Moreover, they are also particularly important building blocks in synthetic organic chemistry.[3] As a consequence, it is not surprising that a large number of effective synthetic methods for the formation of functionalized furans have been specifically designed.[4] In recent years, transition-metal-mediated cycloisomerization reaction of allene derivatives has been shown to be a powerful synthetic method for the preparation of furans.[5,6] In those transformations, the allenyl moieties are activated by transition-metal catalysts (Scheme 1, eq 1). Additionally, access to this class of compounds by an intermolecular approach whereby the two substituents originate from different simple starting materials would have advantages over traditional strategies.[7] As an example, Ellman and co-workers recently reported a general strategy to access substituted furans via a Rh or Co catalyzed alkenyl C−H bond addition to aldehydes (Scheme 1, eq 2).[8] Consequently, the development of a facile and environmentally attractive strategy for the direct intermolecular [3 + 2] annulation of easily available compounds without assistance of metal system is highly desirable.

Dithianes represent a highly valuable class of compounds found in natural product synthesis and synthetic intermediates.[9] As part of an ongoing research program aimed at developing new methods for the synthesis of functionalized dithianes,[10] we recently reported that metal-free couplings of β-chloro-vinyl dithianes with a variety of related nucleophiles can be achieved under mild conditions (Scheme 1, eq 4).[10e] In addition, we have been able to characterize a more reactive vinylidene dithiane facilitated by a stoichiometric amount of base to induce the elimination of HCl.[11] This unique investigation provided a proof of principle for vinylidene dithiane as a reactive acceptor/donor intermediate induced coupling reaction. However, Oh group recently disclosed a mild base-promoted vinylogous aldol-type reaction of β-chlorovinyl ketones through an allenol/cumulenol-(ate) intermediate (Scheme 1, eq 3).[12] However, to the best of our knowledge, direct additions of β-chloro-vinyl dithianes to aldehydes are unknown; the synthetic versatility of vinylidene dithiane as a donor allene has scarcely been studied.[13] Herein, we report a practical and highly efficient [3 + 2] cycloaddition of β-chloro-vinyl dithianes to aldehydes leading to the construction of highly substituted furans. This represents the first example of synthesis of furans in which vinylidene dithianes were used as the

Scheme 1. Novel Strategies for Multisubstituted Furans



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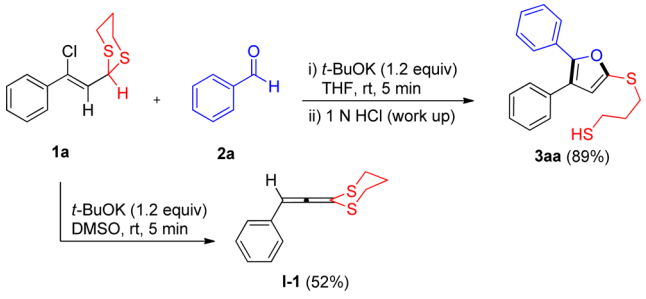
electron-donor moieties for in situ use in the intermolecular [3 + 2] cycloaddition.

In our approach to furan synthesis, we reasoned that the intermolecular [3 + 2] cycloaddition strategy could offer direct access to highly substituted dihydrofurans that are amendable to further aromatization by acid neutralized workup. In the cyclization process, dithiane motif has the ability to "pump" in which the transformation is determined by the relative propensity of the vinylidene dithiane to participate in the electron-transfer process, followed by a vinylogous addition to aldehydes. Most importantly, the development of method may address the regiochemistry problem in cyclization reaction. Meanwhile, the dithiane moiety plays a key role in driving the essential aromatization *in situ* via a standard neutralized workup.

To test our hypothesis, we investigated the reaction of *β*-chloro-alkenyl dithiane **1a** as a standard substrate and benzaldehyde **2a** (Scheme 2). An initial examination of the

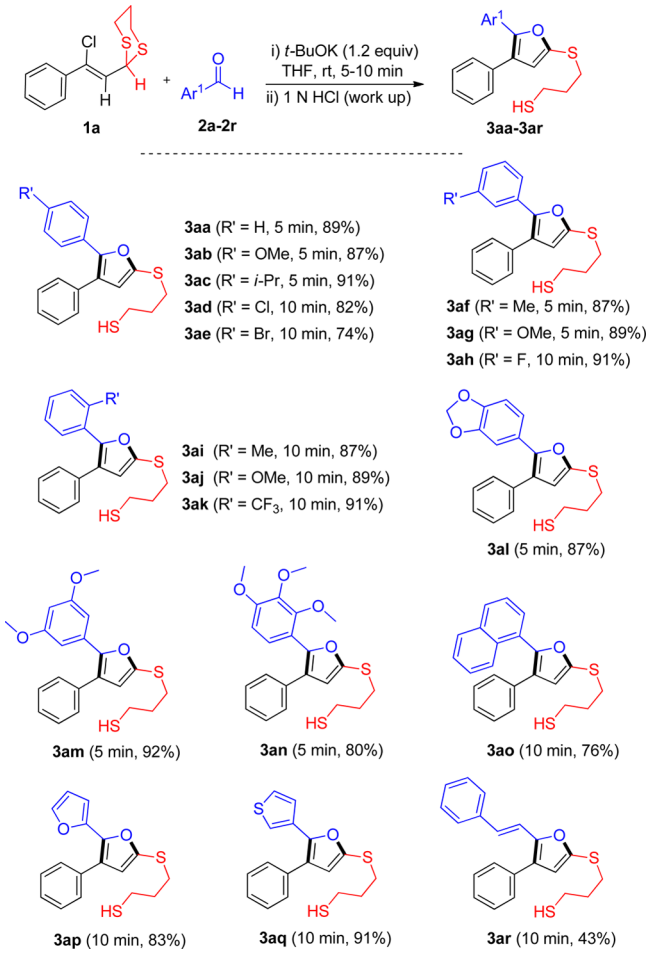
Scheme 2. Standard Reaction Conditions for Multisubstituted Furans



base-mediated reaction conditions revealed that using 1.2 equiv of *t*-BuOK and DMSO as the solvent gave complete conversion of the starting materials at room temperature, and to our delight, we were able to isolate the 2,3,5-trisubstituted furan product **3aa** in 73% yield after standard workup. In DMSO, the examination of other bases such as NaOMe, KOH and NaH was found to be effective for this transformation, while the use of K_2CO_3 was ineffective. It should also be noted that the use of Cs_2CO_3 at 50 °C gave the product in a comparable yield after 2 h (see Table S1 in the Supporting Information (SI)). With the result in hand, we proceeded with screening of different commonly employed solvents. It showed that the yield could be increased to an excellent 89% with THF instead of DMSO (see Table S2 in SI for further information). Moreover, the reaction in THF reached full conversion within 5 min. Notably, the reaction without an aldehyde present at room temperature afforded the reactive vinylidene dithiane **I-1** in moderate isolated yield.[11]

With a set of optimized reaction conditions in hand, we then examined the substrate scope with respect to the aldehyde component. The results are summarized in Scheme 3. Pleasingly, it was found that a variety of functionalized aryl aldehydes could be employed for the formation of furan product efficiently. Substitutions are well tolerated at the 4-position (**3ab**–**3ae**), 3-position (**3af**–**3ah**), and the 2-position (**3ai**–**3ak**), typically giving the 2,3,5-trisubstituted furans in excellent yield after an acidic workup. This aromatic ring was found to be tolerant of both electron-rich groups, such as methyl (**3af** and **3ai**) and methoxy (**3ab**, **3ag**, **3aj**, **3am**, and **3an**), and electron-deficient groups, such as trifluoromethyl (**3ak**). Importantly, the halogen-containing motifs, such as F (**3ah**), Cl (**3ad**), and Br (**3ae**) worked well in this transformation. To this end, several

Scheme 3. Substrate Scope of Aldehydes[a]



[a]Isolated yield. Reaction conditions: (i) **1a** (58 mg, 0.225 mmol), **2a**–**2r** (0.25 mmol), *t*-BuOK (28 mg, 0.25 mmol), THF (2 mL), 5–10 min (ii) 1 N HCl work up.

heteroaryl (**3ap** and **3aq**) and vinyl-substituted (**3ar**) substances were also subjected to furan products. Unfortunately, alkyl aldehydes such as *t*-butyl and *n*-butyl aldehydes remain challenging substrates for this methodology under the current conditions.

Next, a variety of dithiane derivatives with different substitutions (**1b**–**1h**) were synthesized and used to investigate the influence of electronic parameters on the transformation. To our delight, the reactions proceeded well under the optimized reaction conditions, thus affording versatile furan products in good to excellent yields. The substituent on the aromatic ring has little influence on this reaction. Both electron-donating and electron-withdrawing groups were well tolerated in this transformation (Scheme 4). We next tried to extend this methodology to the analogues of dithioacetal. The substrate **1j** underwent the desired cycloaddition and aromatization cascade process in the standard condition and provided the corresponding trisubstituted furans in satisfactory yields.

In probing the intermediates of the reaction, we were pleased to find that the furan product resulted from the corresponding dihydrofuran adduct by an irreversible aromatization.[14] Gratifyingly, the cycloaddition of **1a** with differently aldehydes **2a**–**2m** proceeded smoothly to provide good to high yields of dihydrofurans **4aa**-**4am** with excellent regioselectivities (Table

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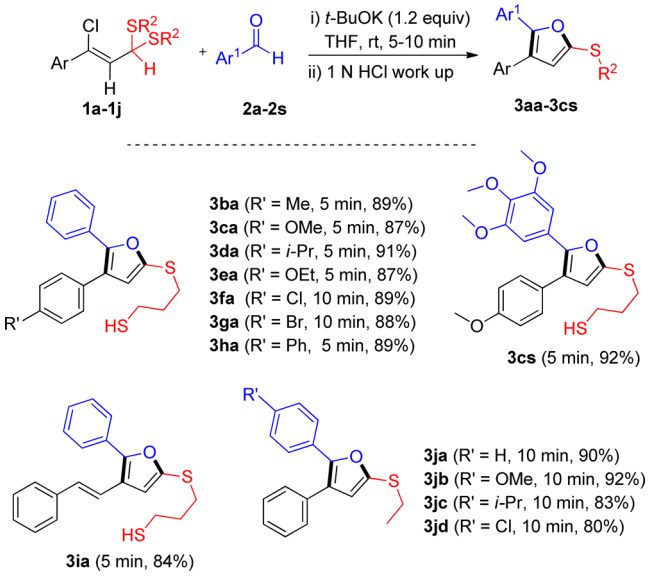
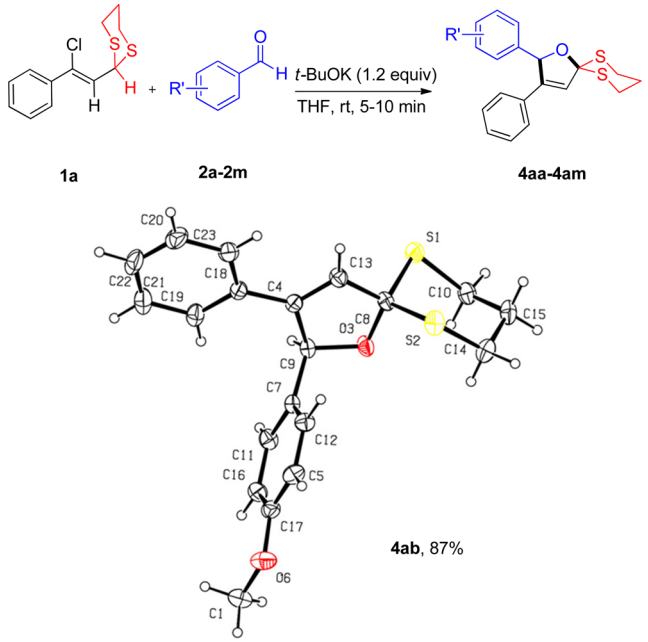
Scheme 4. Substrate Scope of Vinylidene Dithiane Precursors[a]



[a]Isolated yield. Reaction conditions: (i) **1a**−**1j** (0.225 mmol), **2a**−**2s** (0.25 mmol), *t*-BuOK (28 mg, 0.25 mmol), THF (2 mL), 5−10 min (ii) 1 N HCl work up.

1).[6d,e] The assignment of the structure of **4ab** was confirmed by X-ray crystallographic analysis. As indicated by GC/MS and

Table 1. Investigation of Dihydrofurans



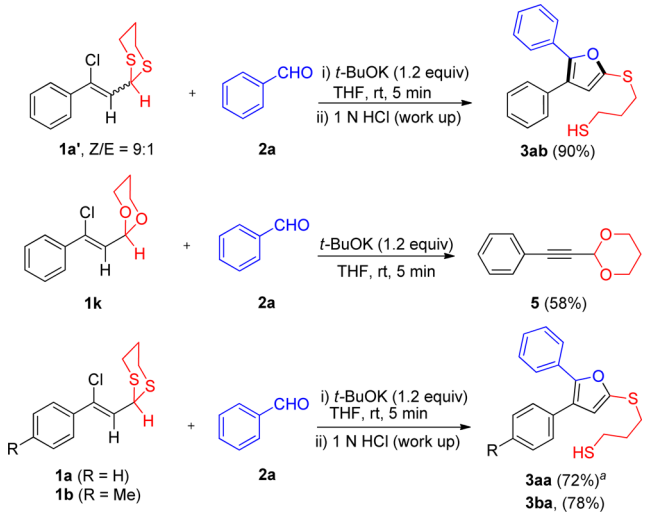
entry	R′	time (min)	product	yield (%)[a]
1	H	5	**4aa**	85
2	4-OMe	5	**4ab**	87
3	4-*i*Pr	5	**4ac**	79
4	2-CF_3	10	**4ak**	84
5	2,5-OMe	5	**4am**	82

[a]Isolated by flash Al_2O_3 column (EA/PE = 1:100−1:25). Reaction conditions: **1a** (58 mg, 0.25 mmol), **2a**−**2m** (0.25 mmol), *t*-BuOK (28 mg, 0.25 mmol), THF (2 mL), 5−10 min.

NMR, the cyclization proceeded to completion without the production of any byproducts.

Alternatively, to gain insights into the dithiane induced annulation process by control experiments, the substrate **1a**′ was independently synthesized and exposed to the standard reaction conditions. As expected, the cycloaddition to **2a** was observed. Conversely, conversions into furan product was not observed when **1k** was used. These results obviously indicated that the dithiane species are required for the cycloaddition processes (Scheme 5).

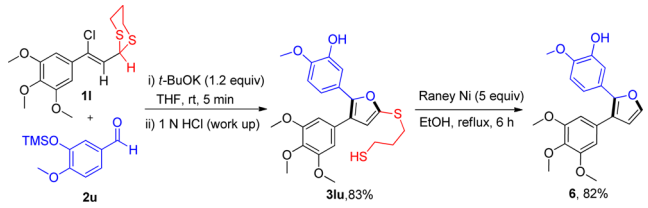
Scheme 5. Mechanistic Experiments and Gram Scale Experiment[a]



[a]Gram scale experiment reaction conditions: (i) **1a**−**1b** (10 mmol), **2a** (1.24 g, 12 mmol), *t*-BuOK (1.4 g, 12 mmol), THF (50 mL), rt, 30 min (ii) 1 N HCl work up.

To illustrate the pharmaceutical utility of our method, we exploited this strategy to conduct the potent rigid combretastatin analogue **6** which displayed a better pharmacokinetic profile to inhibit tubulin assembly (Scheme 6).[15] The [3 + 2] annulation of

Scheme 6. Synthesis of Combretastatin Analogue 6



dithiane **1l** and aldehyde **2u** proceeded well to provide the corresponding furan product **3lu**. Subsequently, furan **3lu** was subjected to a Rainy-Ni mediated reaction to provide the biologically active furan **6** in good yield over the two steps.

In summary, we have developed an extremely mild and efficient method for the preparation of diversely substituted furan scaffolds starting from simple and readily available substrates. The first exploration of dithiane induced cycloadditions with aldehydes has been accomplished without any additional initiators and metal catalyst. The no catalytic method demonstrates a broad range of functional group compatibility. The implementation of the present method to the synthesis of

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other key heterocycles is currently being investigated and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization data for the products, and copies of NMR spectra (PDF)
Crystallographic data for **4ab** (CIF)

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Notes

The authors declare no competing financial interest.

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