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Tandem Transformations via Friedel−Crafts Acylation Followed by a Ring-Expansion, Ring-Opening, and Cycloisomerization Sequence

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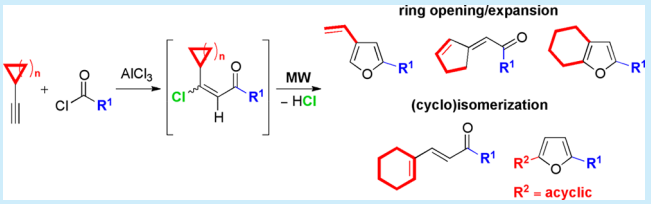
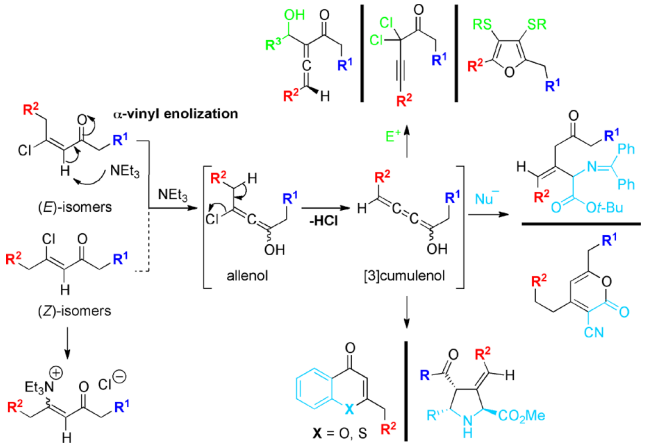
Supporting Information

ABSTRACT: A tandem synthetic route to a diverse array of cyclic compounds has been developed from Friedel−Crafts acylation of alkynes followed by the microwave irradiation of β-chlorovinyl ketone intermediates. The stereoisomeric β-chlorovinyl ketone intermediates smoothly underwent a thermal α-vinyl enolization and ring expansion to vinyl and carbocyclic furans as well as cyclopetene derivatives in good to excellent yields without the need for any catalysts.



β-Chlorovinyl ketones, readily accessible from the Friedel−Crafts acylation of alkynes, represent a special domain of functional molecules with a unique reaction profile and versatile synthetic utility.[1] In contrast to other α,β-unsaturated carbonyl systems, the (*E*)-β-chlorovinyl ketones readily undergo a facile α-vinyl enolization in the presence of a mild base, Et_3N, at ambient temperature (Scheme 1).[2] This reaction

Scheme 1. α-Vinyl Enolization of β-Chlorovinyl Ketones and Their Synthetic Utility



pathway has paved a way to generate versatile synthetic intermediate species with *on demand* reactivity, nucleophilic or electrophilic, where the characteristics of reacting partners could be modulated.[3] The planar conformation of (*Z*)-β-chlorovinyl ketones displays an α-vinyl enolization significantly slower than that of (*E*)-β-chlorovinyl ketones, and the reaction under increased temperature competitively produces the quaternary salts through the Michael addition of Et_3N to (*Z*)-β-chlorovinyl ketones.[2] Thus, at the present time, the synthetic utility of (*Z*)-β-chlorovinyl ketones via the α-vinyl enolization strategy remains largely unexplored.

Motivated by the α-vinyl enolization pathway of β-chlorovinyl ketones, we aimed to discover new synthetic methods that showcase the α-vinyl enolization-driven skeletal rearrangements of β-chlorovinyl ketones. As the conformations of stereoisomeric β-chlorovinyl ketones were projected to influence the initial α-vinyl enolization pathway, the thermal conditions could, in principle, increase access to high-energy conformations/stereoisomers of β-chlorovinyl ketones. Although no previous attempt had been made for such α-vinyl enolization of α,β-unsaturated carbonyl systems,[4] the fact that the alkene isomerization could be performed via conformational and stereochemical changes under thermal conditions strengthened our hypothesis on the thermal α-vinyl enolization of β-chlorovinyl ketones. To capitalize on microwave-assisted superheating methods, β-chlorovinyl ketones were heated under microwave irradiation by varying reaction solvent, temperature, and time (see the Supporting Information for the detailed optimization methods and reaction mechanism studies). The final optimization condition of the thermal α-vinyl enolization of β-chlorovinyl ketones included the irradiation of β-chlorovinyl ketones for 30 min at 250 °C (Scheme 2).

The tandem transformation of acid chlorides **1** and alkyne **2** to furans **3** via the intermediacy of β-chlorovinyl ketones under microwave irradiation was found to be general (Scheme 3). The electronic feature of the acid chloride $\mathbf{R^1}$ did not influence the reaction outcome, providing good to excellent isolated yields of furans **3a**−**3g** over two steps. The structural variation of the alkyne $\mathbf{R^2}$ group was also tolerated where furans with a variety of functional groups such as alkyl chloride **3i**−**j**, ester moiety **3k**, and phthalimide **3l** were smoothly formed. In

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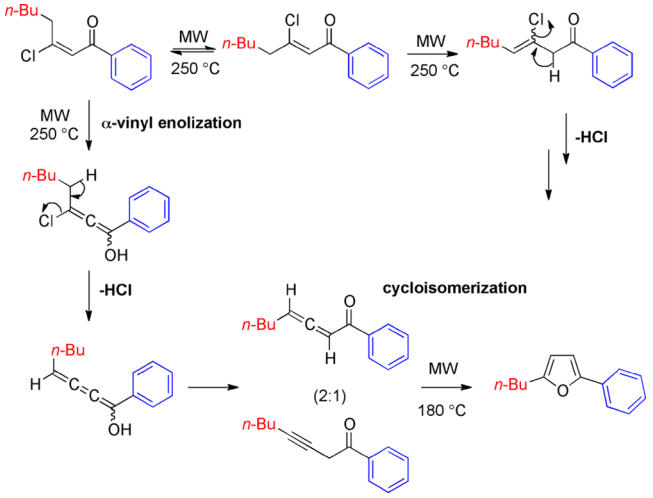
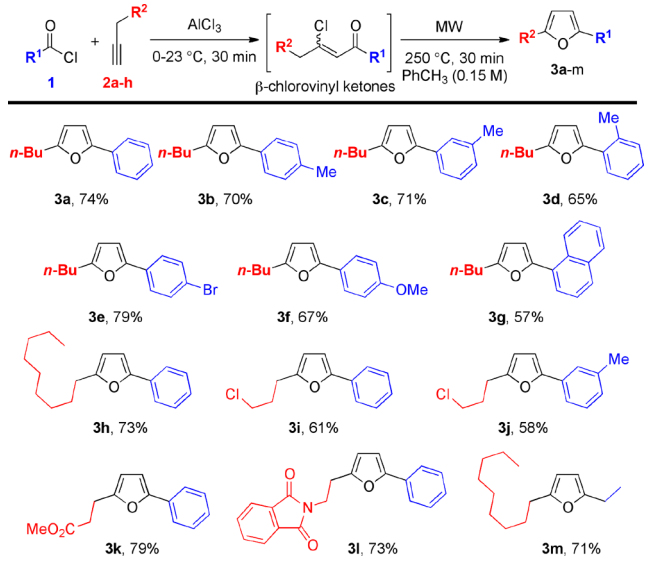
Scheme 2. Thermal α-Vinyl Enolization of β-Chlorovinyl Ketones



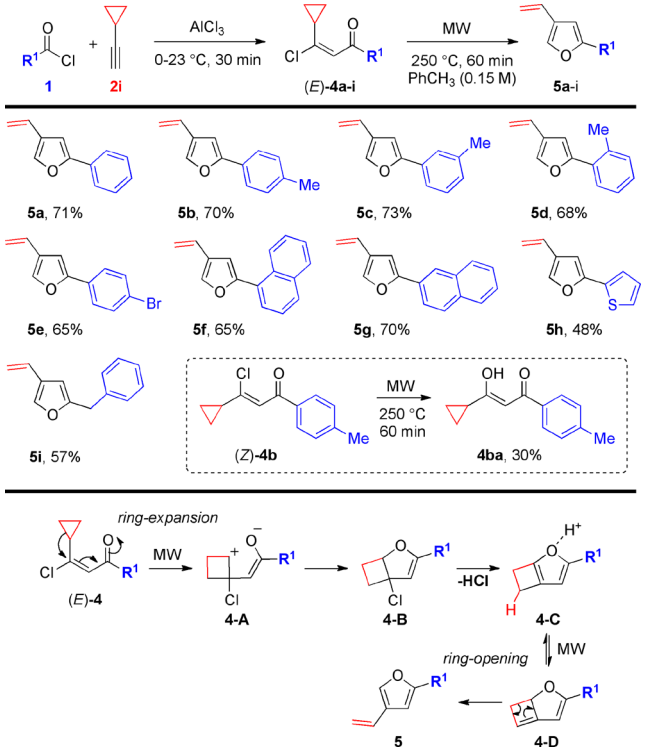
Scheme 3. Enolization and Cycloisomerization Sequence to Furan Derivatives



addition, the introduction of an alkyl group $\mathbf{R^1}$ was also possible, providing a 2,5-dialkyl-substituted furan **3m** in a 71% yield. It should be noted that the current furan synthesis from a mixture of β-chlorovinyl ketones represents a nonmetal, reagentless, and rapid cycloisomerization method development.

Given that the β-chlorovinyl ketones were smoothly transformed to the allenyl ketones under microwave-assisted heating conditions, the β-chlorovinyl ketones with a cyclopropyl group were subjected to the microwave irradiation (Scheme 4). After some experimentation, it was found that (*E*)-β-chlorovinyl ketones **4** with a cyclopropyl group proceeded in the desired tandem reaction sequence to give the corresponding 4-vinylfuran derivatives **5**, whereas the (*Z*)-**4b** only reluctantly underwent water addition reaction to give **4ba** (recovered unreacted (*Z*)-**4b** in 70%). Thus, the cyclopropyl-substituted (*E*)-β-chlorovinyl ketones were isolated and then subjected to microwave irradiation conditions. In this way, a general synthetic route to 4-vinylfuran was established from a tandem reaction sequence from (*E*)-β-

Scheme 4. Ring Expansion and Ring Opening to Furan Derivatives



chlorovinyl ketones in 48−73% yields. Mechanistically, we propose a reaction sequence of the microwave-assisted cyclopropyl opening followed by dehydrochlorination to cyclobutyl-fused furan **4-C**. A subsequent isomerization followed by cyclobutenyl opening under microwave heating conditions leads to 4-vinylfuran product.[5] Previously, the α-substituted 3-cyclopropylideneprop-2-en-1-ones were transformed to furan-fused cyclobutenes under the $PdCl_2$-catalyzed cycloisomerization conditions.[6] Whereas furan-fused cyclobutenes readily opened up the furan moiety under the oxidative conditions (i.e., chemical-driven transformation), the current synthetic access to 4-vinylfurans from (*E*)-β-chlorovinyl ketones maintained the furan moiety, illustrating the unique microwave-assisted heating method.

The introduction of a cyclobutyl group to β-chlorovinyl ketones was next considered because the ring strain of cyclobutanes is comparable to that of cyclopropanes.[7] Starting from the Friedel−Crafts acylation of ethynylcyclobutane **2j**, the subjection of a mixture of β-chlorovinyl ketone intermediates under the microwave irradiation provided a 4:1 mixture of cyclopent-en-1-ylidenes **6** in a synthetically useful level of 48−72% yields (Scheme 5). The ratio of stereoisomers **6** was consistent regardless of the substitution pattern, thus it is conceivable that the equilibrium between (*E*)-**6** and (*Z*)-**6** has been established. One possible driving force to such equilibrium might lie in the isomerization-driven process via **6-D** and **6-E** to the stereoisomeric **6**. Mechanistically, as the possible formation of cyclopentyl-fused furan has been postulated from the corresponding alleneyl ketone upon flash vacuum thermolysis at 800 °C,[8] it is reasonable to speculate the cyclobutane expansion to cyclopentyl-fused furan **6-C** thermally isomerizes to the more stable forms of compounds, cyclopent-en-1-ylidenes **6**. It should be noted that the current

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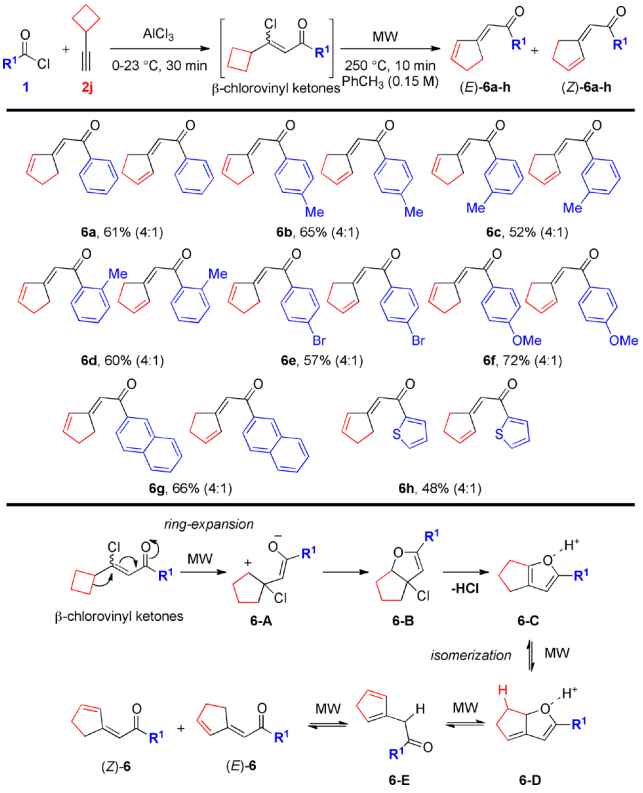
Scheme 5. Ring Expansion to Cyclopent-2-en-1-ylidene Derivatives

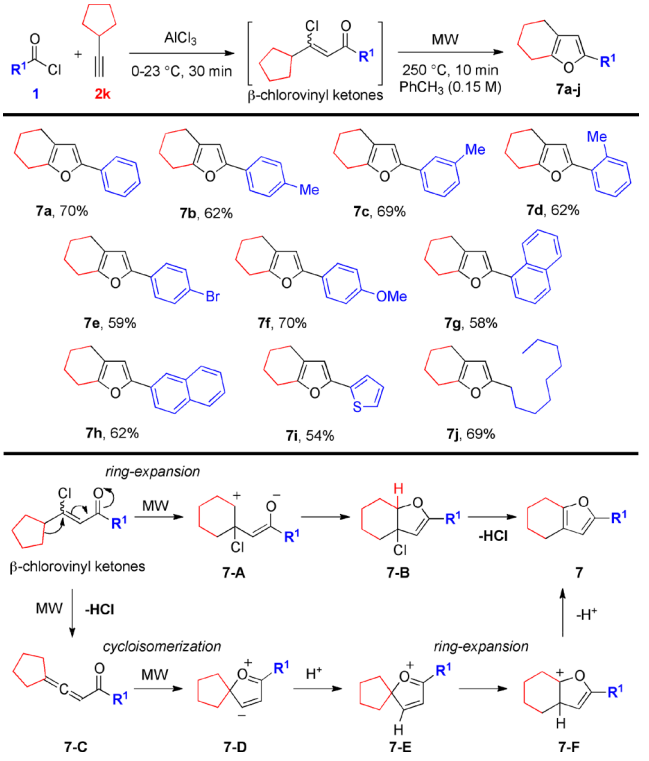


synthetic approach represents a step-economical synthetic method to cyclopent-2-en-1-ylidene derivatives.

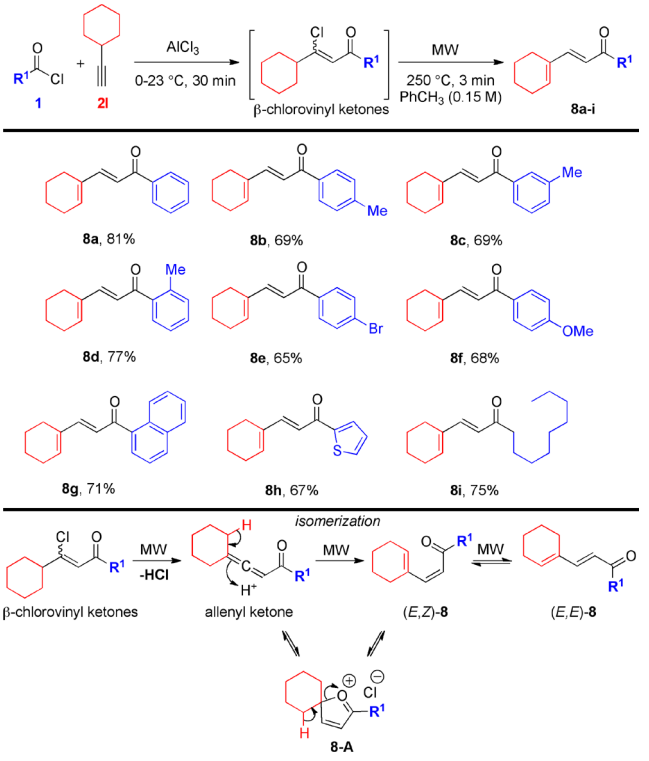
The ring-expansion/isomerization strategy has been extended to β-chlorovinyl ketones with a cyclopentyl group (Scheme 6). Thus, starting from the Friedel–Crafts acylation of ethynylcyclopentane **2k**, the substrate scope of the reaction sequence was broad enough to include a thiophenyl-containing furan **7i** and an alkyl-substituted furan **7j**. The exclusive formation of cyclohexyl-fused furans suggests the involvement of cyclopentyl expansion to **7-B** followed by dehydrochlorination. Also, as our control experiment using cyclopentyl-substituted allenyl ketone **7-C** confirmed the facile cycloisomerization pathway to cyclohexyl fused furan **7a** under the microwave heating conditions at 180 °C, the vinyl enolization of β-chlorovinyl ketones followed by cycloisomerization pathway is equally possible. In contrast to the gold-catalyzed cycloisomerization of allenyl ketones to cyclohexyl-fused furans,[9] the microwave-assisted heating conditions smoothly cycloisomerize cyclopentyl-substituted allenyl ketones to cyclohexyl-fused furans **7** via a thermal ring-expansion strategy.[10]

The use of cyclohexyl-substituted β-chlorovinyl ketones did not provide the ring-expansion/cycloisomerization products. Instead, the formation of dienyl ketones (*E*,*E*)-**8** was accomplished in 65–81% yields (Scheme 7).[11] As our control experiment confirmed a facile isomerization of cyclohexyl-substituted allenyl ketone to dienyl ketone (*E*,*E*)-**8a** under microwave-assisted heating conditions in 3 min, a plausible reaction pathway to dienyl ketones from β-chlorovinyl ketones is presented. Thus, after the Friedel–Crafts acylation of ethynylcyclohexane **2l**, the dehydrochlorination of β-chlorovinyl ketones provides the cyclohexyl-substituted allenyl

Scheme 6. Ring Expansion/Cycloisomerization to Cyclohexyl-Fused Furans



Scheme 7. Isomerization to Dienyl Ketones



ketones, undergoing either the thermal isomerization to dienyl ketones **8** or the cycloisomerization-driven isomerization via **8-A** to dienyl ketone **8**. Whereas the indium-catalyzed cycloisomerization of cyclohexyl-substituted allenyl ketone to cycloheptyl-fused furan has been reported to be 18% by

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NMR,[12] our control experiment using an authentic sample of cyclohexyl-substituted allenyl ketone (R^1 = Ph) did not provide cycloheptyl-fused furan under microwave conditions. Exclusive formation of stereodefined dienyl ketones (*E*,*E*)-**8** from the cyclohexyl-substituted allenyl ketones illustrates the thermodynamic control under microwave-assisted heating conditions.

In summary, we developed tandem synthetic transformations to a diverse array of building blocks from readily available starting materials, alkynes and acid chlorides. With the discovery of a microwave-assisted thermal α-vinyl enolization of β-chlorovinyl ketones, the developed synthetic protocol enables a rapid synthetic transformation of stereoisomeric β-chlorovinyl ketones using ring-expansion, ring-opening, and cycloisomerization strategies. The use of β-chlorovinyl ketones under microwave-assisted heating conditions opens a new venue for rapid and reagentless synthetic transformations with short reaction times and clean reaction profiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03881.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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