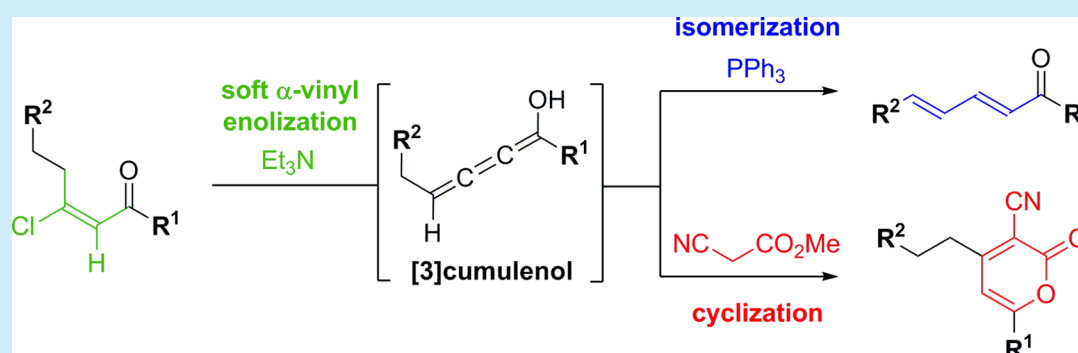


1,3-Dienones and 2H-Pyran-2-ones from Soft α -Vinyl Enolization of β -Chlorovinyl Ketones: Defined Roles of Brønsted and Lewis Base

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S Supporting Information

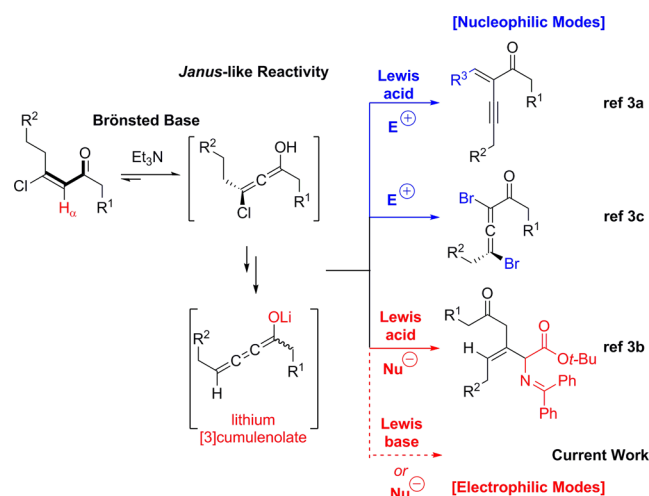


ABSTRACT: The eliminative reaction pathways of (*E*)- β -chlorovinyl ketones were investigated in the presence of both Brønsted and Lewis bases. The Brønsted base, Et_3N , effected the soft α -vinyl enolization of (*E*)- β -chlorovinyl ketones to [3]cumulenol intermediates; in turn, a catalytic amount of Lewis base, PPh_3 , initiated isomerization to provide 1,3-dienones in high yields. The introduction of a carbon-based nucleophile into the reaction mixture provided the highly efficient synthetic route to 2H-pyran-2-ones in one pot, where the carbon-based nucleophile generated by an extra equivalent of Brønsted base, Et_3N , attacked the electrophilic [3]cumulenol intermediates to initiate cyclization to give 2H-pyran-2-ones.

The development of a chemical species that displays multiple reaction pathways remains one of the primary goals in the field of organic chemistry.¹ The recently demonstrated ambivalent reactivity of β -chlorovinyl ketones has opened up new divergent reaction pathways of α,β -unsaturated carbonyl compounds beyond the typical nucleophilic addition reactions to enones (Scheme 1).² The fact that the ambivalent reactivity of β -chlorovinyl ketones enables facile access to stereochemically and structurally diverse products strongly suggests that β -chlorovinyl ketones possess high synthetic potential in an integral part of new reaction discovery and development.³ With an aim of utilizing the soft α -vinyl enolization of β -chlorovinyl ketones, we previously investigated the use of a Lewis acid to promote the addition of glycines to metal [3]cumulenolate intermediate species.^{3b} Motivated by the electrophilic nature of metal [3]cumulenolates from the soft α -vinyl enolization of β -chlorovinyl ketones under Lewis acid conditions, we became interested in the reaction mode of [3]cumulenol intermediates in the absence of a Lewis acid. In this report, we present strong evidence for the electrophilic modes of [3]cumulenol intermediates under Lewis base conditions (or in the presence of a nucleophile).

1,3-Dienones are versatile synthetic intermediates in conjugate addition,⁴ cycloaddition,⁵ and Diels–Alder reactions.⁶ While there are established synthetic methods using the traditional condensation and Wittig reactions,⁷ the develop-

Scheme 1. Soft α -Vinyl Enolization-Induced Janus-like Reactivity of β -Chlorovinyl Ketones



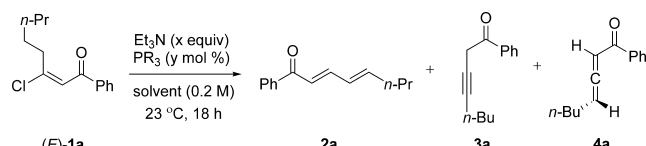
ment of more direct synthetic methods to 1,3-dienones has been the subject of intense investigation. Metal-catalyzed cross-coupling reactions⁸ as well as cross-metathesis approaches

Received: November 12, 2015

provide an array of diversely substituted 1,3-dienones.⁹ Moreover, phosphine-catalyzed isomerizations of electron-poor alkynes to 1,3-dienones have been pioneered by Trost¹⁰ and Lu,¹¹ respectively. While the tandem elimination/isomerization of enol triflates under palladium catalysis has been recently disclosed by Frantz,¹² there are no other examples that employ α,β -unsaturated ketones as precursors to 1,3-dienones. Herein, we report a facile one-pot synthesis of 1,3-dienones from the soft α -vinyl enolization of β -chlorovinyl ketones in the presence of both Brønsted and Lewis bases with distinctively defined roles.

To evaluate the compatibility of the Lewis base with the soft α -vinyl enolization conditions of β -chlorovinyl ketones, we investigated the potential use of phosphines as a Lewis base (Table 1). Thus, our previously optimized soft α -vinyl

Table 1. Optimization of 1,3-Dienones from (*E*)- β -Chlorovinyl Ketones



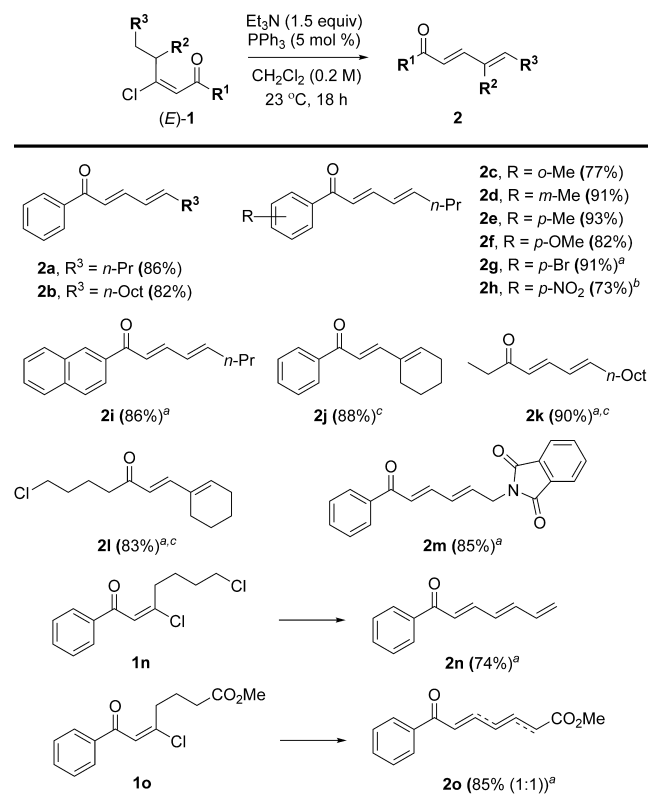
entry	Et ₃ N, <i>x</i> equiv	PR ₃ , <i>y</i> mol %	solvent	2a, yield ^a (%)
1	1.1	PPh ₃ , 10	CH ₂ Cl ₂	2a, 73 ^b
2	1.5	PPh ₃ , 10	CH ₂ Cl ₂	2a, 87
3	1.5	PPh ₃ , 10	THF	2a, 67 ^b
4	1.5	PPh ₃ , 10	CH ₃ CN	2a, 79
5	1.5	P(^{<i>t</i>} Bu) ₃ , 10	CH ₂ Cl ₂	^c
6	1.5	PPh ₃ , 5	CH ₂ Cl ₂	2a, 86
7	1.5	PPh ₃ , 3	CH ₂ Cl ₂	2a, 51 ^d
8		PPh ₃ , 10	CH ₂ Cl ₂	2a, 0

^aIsolated yield of **2a** after column chromatography. ^bUnreacted (*E*)-**1a** was recovered. ^cA 1:2 mixture of **3a** and **4a** was isolated in 90% yield. ^dThe remaining molecular mass balance accounts for a 1:2 mixture of **3a** and **4a**.

enolization of (*E*)- β -chlorovinyl ketone **1a** was performed in the presence of PPh₃ (10 mol %). To our delight, the formation of 1,3-dienone **2a** was obtained in 73% yield with about 80% reaction conversion (entry 1). The use of 1.5 equiv of Et₃N led to the full consumption of **1a**, providing 87% yield of **2a** (entry 2). Solvents that are suitable mediums for the soft α -vinyl enolization were investigated; however, the reaction in THF led to a lower reactivity (entry 3) and the use of CH₃CN provided a slightly diminished yield of **2a** in 79% (entry 4). Interestingly, the use of P(^{*t*}Bu)₃ under our reaction conditions did not provide **2a** (entry 5).¹³ Lowering the amount of PPh₃ to 5 mol % did not affect the observed yields of **2a**, although the employment of 3 mol % did result in a mixture of unreacted propargyl ketone **3a** and allenone **4a** (entries 6 and 7). The control experiments also confirmed that (*E*)- β -chlorovinyl ketone **1a** did not react with PPh₃ (entry 8).

Scheme 2 shows the generality of our one-pot synthesis of 1,3-dienones from a soft α -vinyl enolization of β -chlorovinyl ketones. The reaction was widely applicable to various substrates (*E*)-**1** with electronically as well as sterically diverse substituents (**2a–i**). The preparation of substituted alkene **2j**, α -alkyl-1,3-dienone **2k**, and functionalized 1,3-dienones **2l,m** was achieved under the optimized reaction conditions. (*E*)- β -Chlorovinyl ketone **1n** with a chlorine atom four carbons away from the enone moiety smoothly underwent the desired

Scheme 2. Scope of the One-Pot Synthesis of 1,3-Dienones

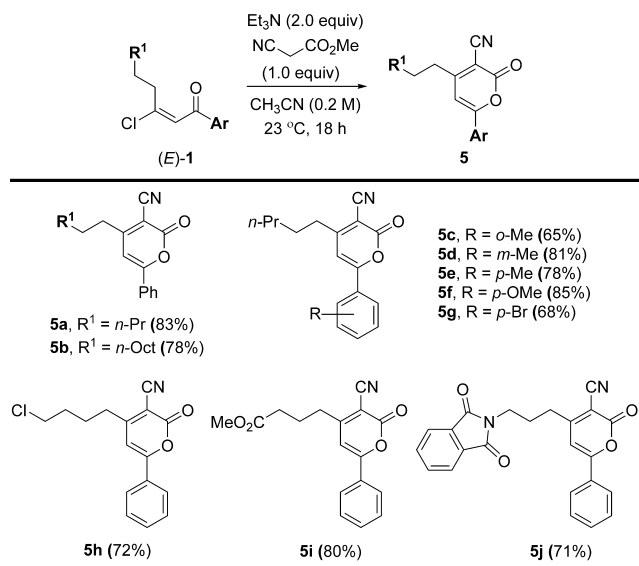
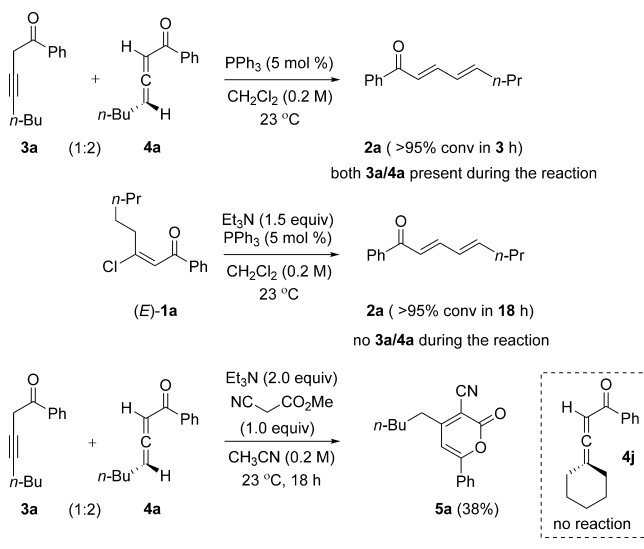


^aPPh₃ (10 mol %). ^bPPh₃ (50 mol %) at 0 °C for 3 h. ^cReaction at 83 °C.

reaction to provide 1,3,5-trienone **2n** in 74% yield. In addition, a substrate **1o** with an enolizable ester moiety provided a 1:1 mixture of 1,3-dienone and 1,3-dienyl ester in 85% yield. It should be noted that the current one-pot synthesis of 1,3-dienones from α,β -unsaturated ketones demonstrates the compatibility between a Brønsted base (Et₃N) and a Lewis base (PPh₃) during the reaction.

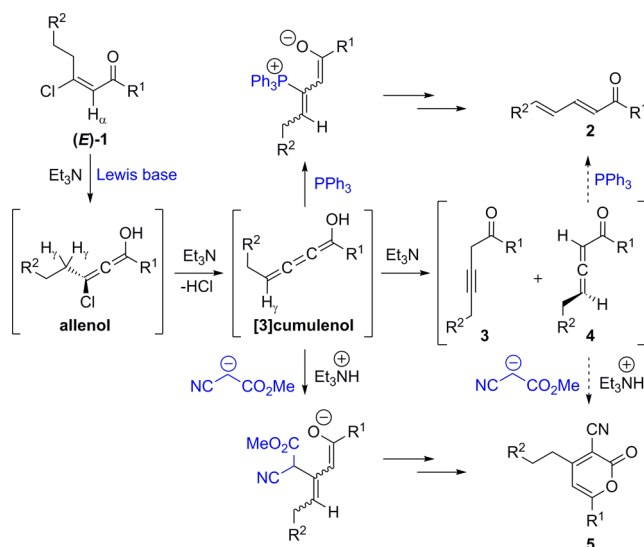
The defined roles of Brønsted and Lewis bases in the one-pot synthesis of 1,3-dienones strongly imply that a nucleophile could be utilized in the tandem soft α -vinyl enolization and conjugate addition reaction sequence. Thus, based on the pK_a of Et₃N, we investigated the use of methyl cyanoacetate (pK_a 12.8) as a potential nucleophile. Gratifyingly, a simple mixing of (*E*)-**1**, methyl cyanoacetate **5**, and 2 equiv of Et₃N in CH₃CN provided a facile synthetic route to 2*H*-pyran-2-ones **5a–j** in 71–85% yields (Scheme 3).¹⁴ At the present time, the one-pot synthesis of 2*H*-pyran-2-ones from (*E*)- β -chlorovinyl ketones is limited to nonenolizable (*E*)-**1**, possibly due to the competing enolization of an alkyl group.¹⁵

To elucidate the electrophilic species, a mixture of propargyl ketone **3a** and allenone **4a** was treated with PPh₃ (5 mol %) (Scheme 4). A full conversion of the mixture to 1,3-dienone **2a** took 3 h at ambient temperature, while the consumption of **3a** and **4a** could be monitored. Next, we monitored the reaction of (*E*)- β -chlorovinyl ketone **1a** at several intervals; however, the presence of propargyl ketone **3a** and allenone **4a** could not be confirmed. Our experimental observations suggest that the major pathway to 1,3-dienones from (*E*)- β -chlorovinyl ketones is likely the result of the PPh₃-catalyzed isomerization of [3]cumulenol species. More experimental support for the

Scheme 3. One-Pot Synthesis of 2*H*-Pyran-2-onesScheme 4. Involvement of [3]Cumulenol Species during One-Pot Synthesis of 1,3-Dienones and 2*H*-Pyran-2-ones

involvement of electrophilic [3]cumulenol species was obtained upon using methyl cyanoacetate as a nucleophile. Thus, the treatment of a mixture of propargyl ketone **3a** and allenone **4a** with Et_3N and methyl cyanoacetate resulted in the formation of 2*H*-pyran-2-one **5a** in 38% yield. Similarly, the trisubstituted allenone **4j** failed to undergo the desired cyclization to 2*H*-pyran-2-ones even at elevated reaction temperature. The use of (*Z*)-**1a** led to the formation of 1,3-dienone **2a** and 2*H*-pyran-2-one **5a** in 20–25% yields within 18 h, corresponding to the kinetics of the soft α -vinyl enolization of (*Z*)-**1a**.²

While the possibility of stepwise reaction pathways, involving the PPh_3 -assisted isomerization of allenones **4** to 1,3-dienones or the conjugate addition of methyl cyanoacetate to allenones **4** followed by an intramolecular cyclization to 2*H*-pyran-2-ones, could not be completely ruled out, our data suggested that the major pathways to 1,3-dienones and 2*H*-pyran-2-ones involved the electrophilic [3]cumulenol species, as we observed for the reaction between metal [3]cumulenolates and glycines (Scheme 5).^{3b}

Scheme 5. Major Reaction Pathways in a One-Pot Access to 1,3-Dienones and 2*H*-Pyran-2-ones

In summary, we developed a one-pot synthesis of 1,3-dienones and 2*H*-pyran-2-ones from the soft α -vinyl enolization of β -chlorovinyl ketones in the presence of both Brønsted and Lewis bases. Complementary to the electrophilic mode of metal [3]cumulenolate species under Lewis acid conditions, the electrophilic reaction pathway of [3]cumulenol species under Lewis base conditions reinforces the divergent and ambivalent reaction pathways of β -chlorovinyl ketones, paving the way for synthetically useful transformations. We are currently exploring the divergent reaction pathways of β -chlorovinyl ketones using other electrophiles and nucleophiles, and our results will be reported in due course.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03265.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2015R1A5A1008958).

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(13) No reaction was observed upon treating a mixture of propargyl ketone and allenone with P(^tBu)₃ at ambient temperature for 24 h.

(14) The use of 1 equiv Et₃N resulted in an uncompleted reaction with 50–60% conversion.

(15) The use of alkyl-substituted β -chlorovinyl ketones resulted in the formation of propargyl ketone and allenone. No cyclization products **5** were observed.