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

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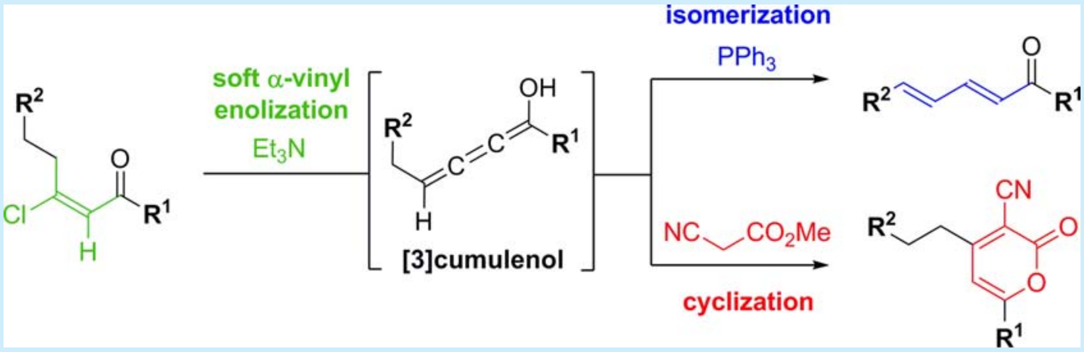
Supporting Information

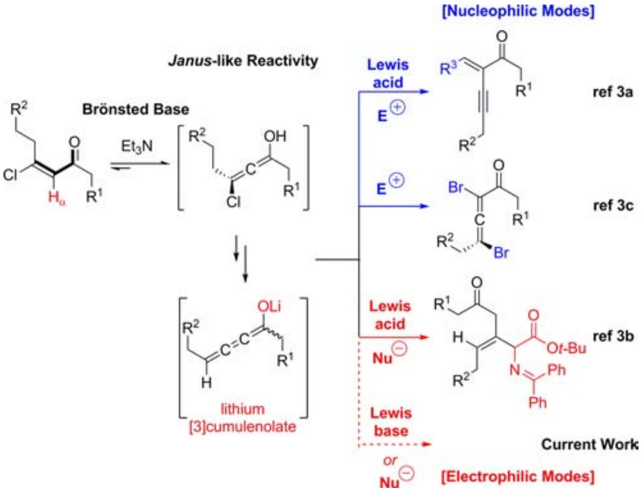


ABSTRACT: The eliminative reaction pathways of (*E*)-*β*-chlorovinyl ketones were investigated in the presence of both Brönsted and Lewis bases. The Brönsted base, Et$_3$N, effected the soft *α*-vinyl enolization of (*E*)-*β*-chlorovinyl ketones to [3]cumulenol intermediates; in turn, a catalytic amount 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 2*H*-pyran-2-ones in one pot, where the carbon-based nucleophile generated by an extra equivalent of Brönsted base, Et$_3$N, attacked the electrophilic [3]cumulenol intermediates to initiate cyclization to give 2*H*-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 glycinates 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 development of more direct synthetic methods to 1,3-dienones has been the subject of intense investigation. Metal-catalyzed cross-coupling reactions[8] as well as cross-metathesis approaches

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



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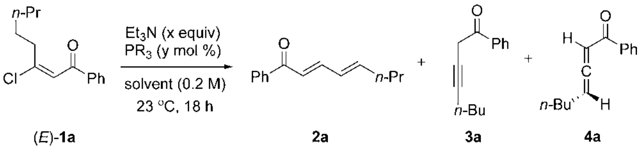
provide an array of diversely substituted 1,3-dienones.[9] Moreover, phosphine-catalyzed isomerizations of electron-poor alkynes to 1,3-dienones have been pioneered by Trost[10] and Lu,[11] respectively. While the tandem elimination/isomerization of enol triflates under palladium catalysis has been recently 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 Brönsted 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 enolization of (E)-β-chlorovinyl ketone **1a** was performed in the presence of PPh_3 (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 Et_3N 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 CH_3CN provided a slightly diminished yield of **2a** in 79% (entry 4). Interestingly, the use of $P(^{n}Bu)_3$ under our reaction conditions did not provide **2a** (entry 5).[13] Lowering the amount of PPh_3 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 PPh_3 (entry 8).

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

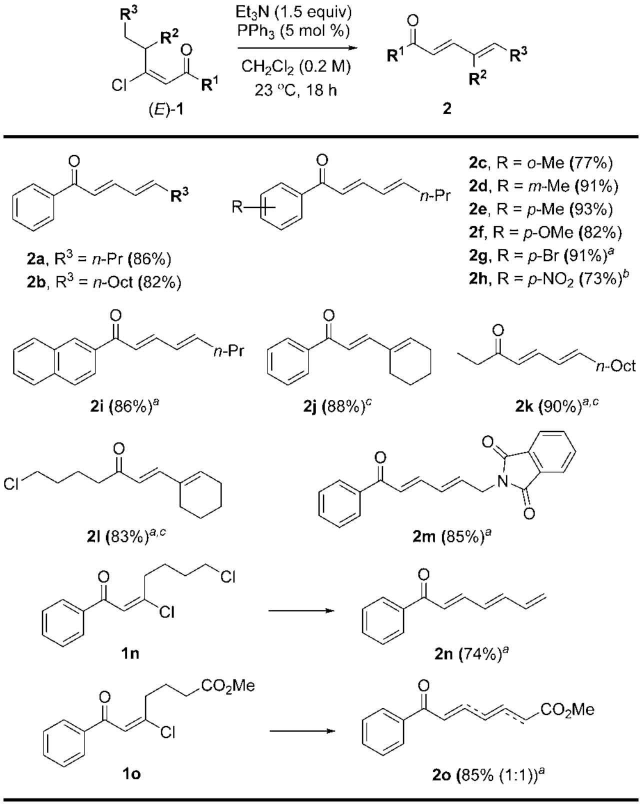


entry	Et_3N, x equiv	PR_3, y mol %	solvent	**2a**, yield[a] (%)
1	1.1	PPh_3, 10	CH_2Cl_2	**2a**, 73[b]
2	1.5	PPh_3, 10	CH_2Cl_2	**2a**, 87
3	1.5	PPh_3, 10	THF	**2a**, 67[b]
4	1.5	PPh_3, 10	CH_3CN	**2a**, 79
5	1.5	$P(^{n}Bu)_3$, 10	CH_2Cl_2	[c]
6	1.5	PPh_3, 5	CH_2Cl_2	**2a**, 86
7	1.5	PPh_3, 3	CH_2Cl_2	**2a**, 51[d]
8		PPh_3, 10	CH_2Cl_2	**2a**, 0

[a] Isolated yield of **2a** after column chromatography. [b] Unreacted (E)-**1a** was recovered. [c] A 1:2 mixture of **3a** and **4a** was isolated in 90% yield. [d] The remaining molecular mass balance accounts for a 1:2 mixture of **3a** and **4a**.

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 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 Brönsted base (Et_3N) and a Lewis base (PPh_3) during the reaction.

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

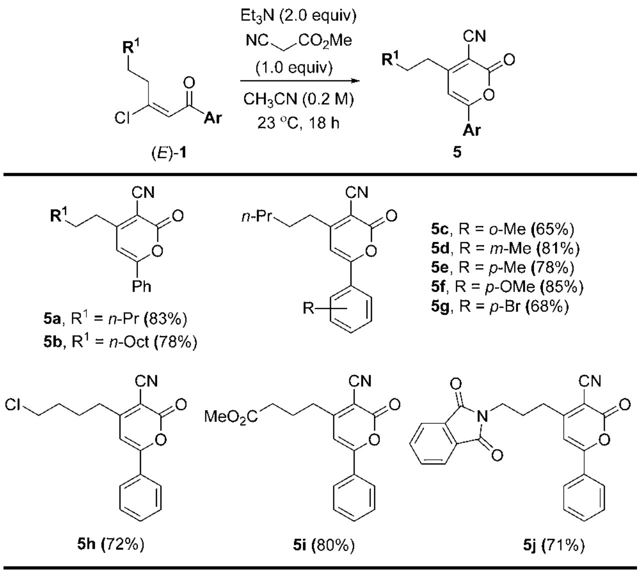


[a] PPh_3 (10 mol %). [b] PPh_3 (50 mol %) at 0 °C for 3 h. [c] Reaction at 83 °C.

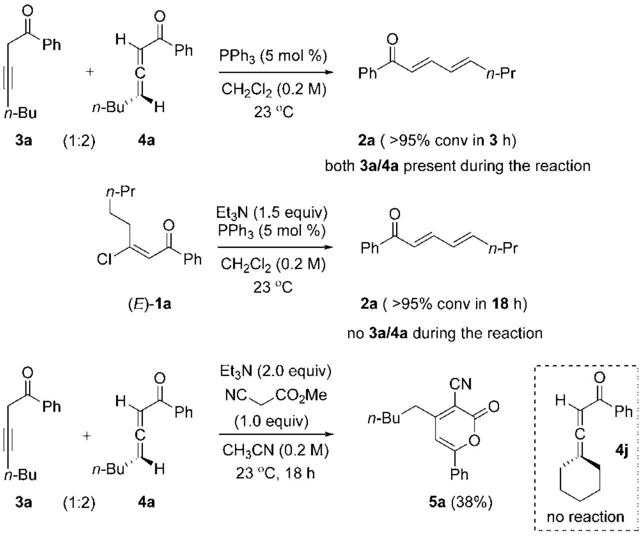
The defined roles of Brönsted and Lewis bases in the one-opt synthesis of 1,3-dienones strongly imply that a nucleophile could be utilized in the tandem soft α-vinyl enolization and conjugate addition reaction sequence. Thus, based on the pK_a of Et_3N, we investigated the use of methyl cyanoacetate (pK_a 12.8) as a potential nucleophile. Gratifyingly, a simple mixing of (E)-**1**, methyl cyanoacetate **5**, and 2 equiv of Et_3N in CH_3CN 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 PPh_3 (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 PPh_3-catalyzed isomerization of [3]cumulenol species. More experimental support for the

Scheme 3. One-Pot Synthesis of 2*H*-Pyran-2-ones



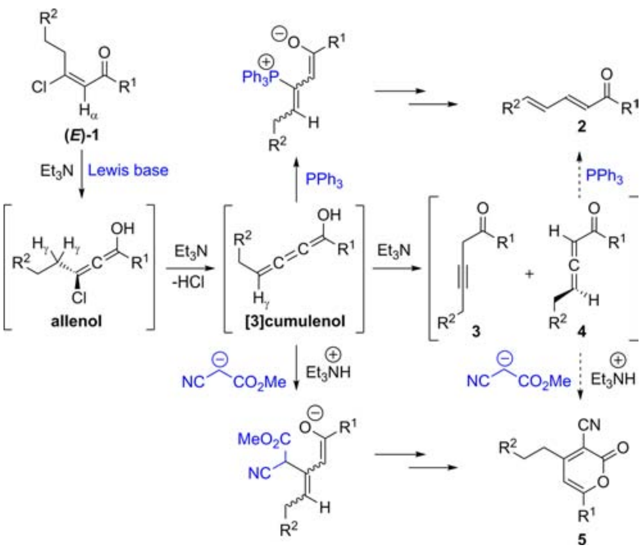
Scheme 4. Involvement of [3]Cumulenol Species during One-Pot Synthesis of 1,3-Dienones and 2*H*-Pyran-2-ones



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$_3$N 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 glycinates (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 Brönsted 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.

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(13) No reaction was observed upon treating a mixture of propargyl ketone and allenone with $P(^{n}Bu)_3$ at ambient temperature for 24 h.

(14) The use of 1 equiv Et_3N 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.