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Phosphine-Catalyzed Synthesis of 6-Substituted 2-Pyrones: Manifestation of *E*/*Z*-Isomerism in the Zwitterionic Intermediate

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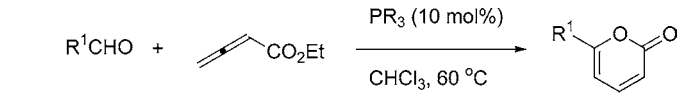
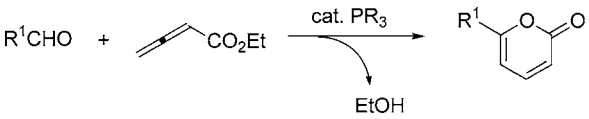
ABSTRACT



R[1] = aryl, alkyl
R = isopropyl, cyclopentyl, cyclohexyl

We report a one-step phosphine-catalyzed annulation between aldehydes and ethyl allenoate to form 6-substituted 2-pyrones. The mechanistic rationale for this reaction requires explicit discussion of the *E*/*Z*-isomerism of the zwitterionic intermediate formed by the addition of a phosphine to the allenoate. Sterically demanding trialkylphosphines facilitate the shift of equilibrium toward the *E*-isomeric zwitterion and lead to the formation of 6-substituted 2-pyrones. Various aromatic as well as aliphatic aldehydes undergo the transformation in moderate to excellent yield.

2-Pyrones[1] are found in a large number of natural products that display biological activities such as anti-HIV,[2] telomerase inhibition,[3] antimicrobial,[4] antifungal,[5] cardiotonic,[6] pheromonal,[7] androgen-like,[8] and phytotoxic[9] effects. Consequently, much attention has been paid to the synthesis of 2-pyrones either by traditional approaches[10] or by transition-metal-catalyzed procedures.[11] Despite the plethora of these synthetic processes, there is a general lack of simple procedures to synthesize 6-substituted 2-pyrones from commercially available starting materials. Herein, we report a one-step phosphine-catalyzed synthesis of 6-substituted 2-pyrones from commercially available starting materials: aldehydes and ethyl allenoate[12] (eq 1).



(1)

Nucleophilic phosphine catalysis of allenoates and butynoates represents a rapidly growing area of research interest

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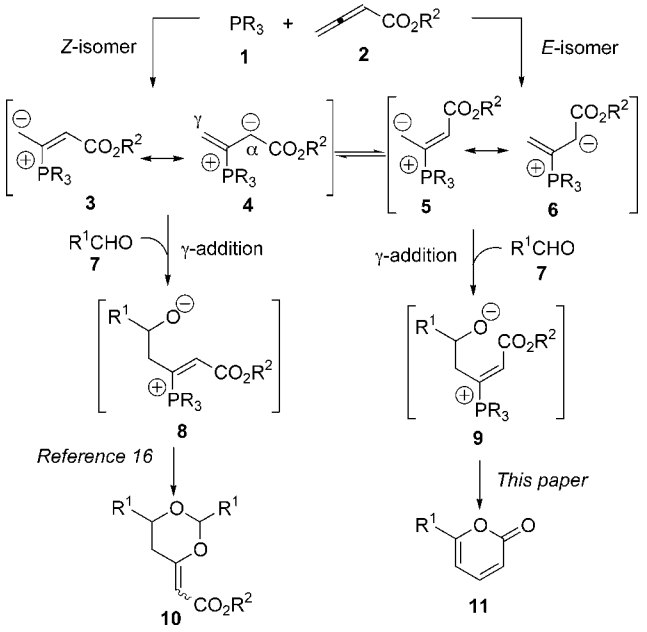
these days.[13] In these reactions, the zwitterionic intermediate, generated by addition of a phosphine to an allenoate, is represented as **3** ↔ **4** (Scheme 1). This zwitterionic intermediate adds to imines exclusively at its α carbon,[14] to electron-deficient alkenes preferably at its α carbon,[15] and to aldehydes exclusively at its γ carbon.[16] Nevertheless, the alternative *E*-isomeric zwitterionic intermediate, **5** ↔ **6**, has not been previously considered. The *E*- or *Z*-geometric information is lost when the zwitterionic intermediate reacts at the α carbon. However, when the addition occurs at the γ carbon as with an aldehyde the geometric distinction in the zwitterionic intermediate is conserved in the resulting adduct (see **8** and **9**). Thus, intermediate **8** incorporates another equivalent of aldehyde and produces dioxanylidene **10**. The close proximity of the alkoxide with respect to the ester group in **9** facilitates intramolecular lactonization and results in the synthesis of 6-substituted 2-pyrone **11**.

Scheme 1. Equilibrium of *E*- and *Z*-Isomers of the Zwitterionic Intermediate Formed by the Addition of a Phosphine to an Allenoate



The *Z*-isomer **3** ↔ **4** is favored due to the electrostatic association between the dienolate oxygen anion and the phosphonium cation.[17] Consequently, we speculated that a dominant steric bias would be needed to shift the equilibrium toward *E*-isomer **5** ↔ **6**. In practice, sterically demanding trialkylphosphines were used to shift the equilibrium toward *E*-isomer **5** ↔ **6** and led to the formation of 6-substituted 2-pyrones (Table 1, entries 1−3). Extremely bulky tri(*tert*-butyl)phosphine produced no product (Table 1, entry 4), and triphenylphosphine provided only 24% of product (Table 1, entry 5). Tributylphosphine did not render any pyrone formation (Table 1, entry 6). When the most efficient tricyclopentylphosphine was used, ethyl allenoate, among alkyl allenoates, provided the highest yield of pyrone (Table 1, entries 7−11). Phenyl allenoate provided no product (Table 1, enytry 12). We speculate that this is due to the diminished basicity of phenoxide, in comparison to alkoxides,

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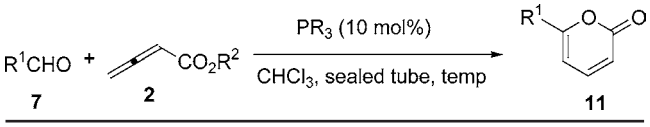
Table 1. Optimization of Conditions for the Synthesis of 2-Pyrones **11a**/**11c** from Alkyl Allenoates and Arylaldehydes[a]



entry	R^{1b}	R	R^{2c}	T (°C)	time	yield[d] (%)
1	3-ClC_6H_4 (**7c**)	*i*-Pr	Et (**2b**)	60	24 h	74
2	3-ClC_6H_4	Cy	Et	60	24 h	77
3	3-ClC_6H_4	Cyp	Et	60	24 h	81
4	3-ClC_6H_4	*t*-Bu	Et	60	24 h	0
5	3-ClC_6H_4	Ph	Et	60	24 h	24
6[e]	3-ClC_6H_4	*n*-Bu	Et	60	24 h	0
7	Ph (**7a**)	Cyp	Me (**2a**)	60	48 h	40
8	Ph	Cyp	Et (**2b**)	60	48 h	60
9	Ph	Cyp	*i*-Pr (**2c**)	60	48 h	39
10	Ph	Cyp	$TMSCH_2$ (**2d**)	60	48 h	58
11	Ph	Cyp	*t*-Bu (**2e**)	60	48 h	10
12	Ph	Cyp	Ph (**2f**)	60	48 h	0
13	3-ClC_6H_4 (**7c**)	*i*-Pr	Et (**2b**)	rt	12 d	57
14[f]	3-ClC_6H_4	*i*-Pr	Et	40	4 d	68
15[f]	3-ClC_6H_4	*i*-Pr	Et	60	49 h	70
16[f]	3-ClC_6H_4	*i*-Pr	Et	84	35 h	63
17[f]	3-ClC_6H_4	*i*-Pr	Et	120	14 h	42

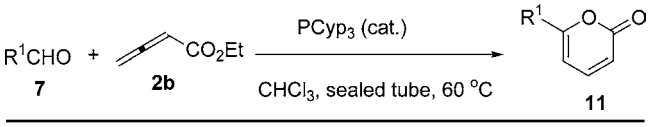
[a] See the Supporting Information for experimental procedures. [b] 5 equiv of 3-chlorobenzaldehyde and 15 equiv of benzaldehyde were used. [c] For the synthesis of various aryl/alkyl allenoates, see the Supporting Information. [d] Isolated yields. [e] 1,3-Dioxan-4-ylidene was formed: see ref 16 for details. [f] 20 mol % of PR_3 was used.

based on our proposed mechanism (vide infra). The reaction was very sluggish at ambient temperature. Pyrone **11c** was obtained in 57% yield after 12 days at room temperature (Table 1, entry 13). The reaction proceeded faster at elevated temperatures providing higher yield of products (Table 1, entries 14−16). However, the product yield decreased at much higher temperatures (Table 1, entry 17).

The optimized conditions were employed to establish the scope of the aldehyde substrates (Table 2). Various aromatic aldehydes bearing electron-withdrawing and electron-donating groups provided 6-aryl 2-pyrones in over 60% yield (Table 2, entries 1−8). 2-Naphthaldehyde and 2-furaldehyde afforded pyrones in 66 and 61% yield, respectively (Table 2, entries 9 and 10). Although reaction yields were moderate for aliphatic aldehydes (Table 2, entries 11 and 12), the reaction provides valuable products in only one step from commercially available aldehydes. For instance, 6-*n*-propyl-2-pyrone (**11l**), which was obtained in 34% yield, possesses creamy, sweet, coumarin-like, and herbal flavor,[18] and is used as an additive to alter the organoleptic properties of tobacco.[19]

Our mechanistic proposal for the reaction is as follows (Scheme 2). When a sterically demanding trialkylphosphine is added to an allenoate, the resulting zwitterionic intermediate exists in the **5** ↔ **6** form rather than the **3** ↔ **4** form to minimize the steric interaction between the phosphonium moiety and the ethoxycarbonyl group. The γ-addition of the vinylphosphonium salt **5** ↔ **6** to an aldehyde forms the intermediate **9** in which the alkoxide moiety is in close proximity to the ester functionality. An intramolecular nucleophilic attack of the alkoxide to the ester furnishes

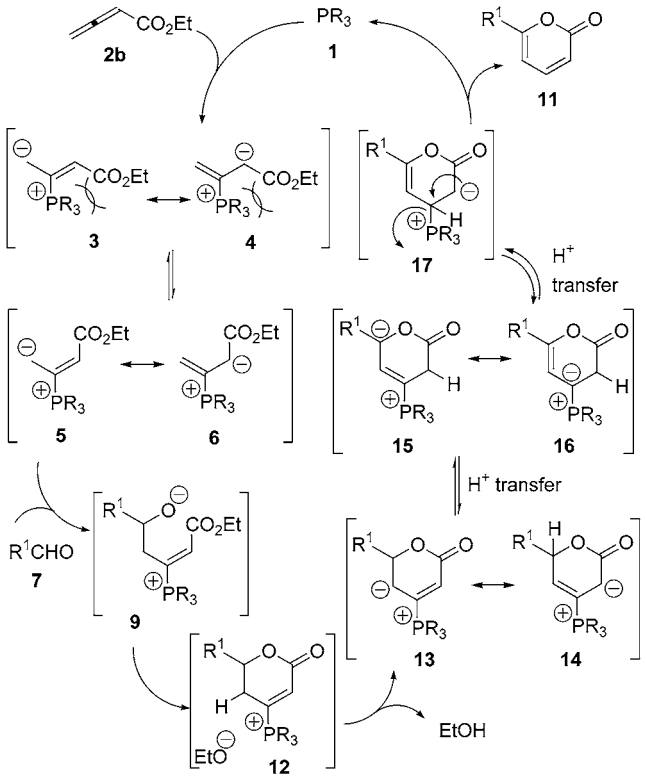
Table 2. Synthesis of 2-Pyrones **11** from Ethyl Allenoate and Aldehydes[a]



entry	R	$PCyp_3$ (mol %)	product	yield[b] (%)
1	Ph (**7a**)	10	**11a**	60
2	3-$MeOC_6H_4$ (**7b**)	20	**11b**	69
3	3-ClC_6H_4 (**7c**)	10	**11c**	91
4	2-ClC_6H_4 (**7d**)	10	**11d**	73
5	4-FC_6H_4 (**7e**)	20	**11e**	68
6	4-CNC_6H_4 (**7f**)	10	**11f**	79
7	4-$CF_3C_6H_4$ (**7g**)	20	**11g**	82
8	2-$CF_3C_6H_4$ (**7h**)	20	**11h**	71
9	2-naphthyl (**7i**)	30	**11i**	66
10	2-furyl (**7j**)	30	**11j**	61
11	2-phenethyl (**7k**)	30	**11k**	39
12	*n*-propyl (**7l**)	30	**11l**	34

[a] See the Supporting Information for experimental procedures. [b] Isolated yields.

Scheme 2. Proposed Mechanism for the Formation of **11**



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lactone intermediate **12**. The resulting ethoxide acts as a base to generate zwitterionic intermediate **13** that is in resonance with **14**. Two consecutive proton-transfer processes produce the intermediate **17**, which dissociates to 2-pyrone **11** and trialkylphosphine.

In conclusion, our effort to expand the scope of phosphine-catalyzed annulations has led us to the rational design of a new reaction to synthesize 6-substituted 2-pyrones from various aldehydes and ethyl 2,3-butadienoate. The rationale behind this reaction was highlighted by the discussion on the *E*/*Z*-isomerism of the zwitterionic intermediate formed by the addition of a phosphine to an allenoate. Sterically demanding trialkylphosphines facilitated the shift of equilibrium toward *E*-isomers and led to the formation of 6-substituted 2-pyrones. This process illustrates the potential of nucleophilic catalysis of allenoates as a fertile ground for the discovery of new reactions.

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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