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Phosphine-Mediated Reductive Condensation of γ-Acyloxy Butynoates: A Diversity Oriented Strategy for the Construction of Substituted Furans

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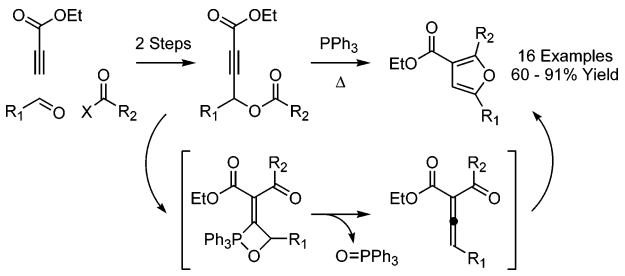
Derivatives of furan occur ubiquitously in nature,[1,2] appear in the structure of diverse therapeutic agents (e.g., ranitidine or zantac), and serve as useful intermediates in organic synthesis.[3] While numerous strategies for furan synthesis exist, convergent annulation strategies are uncommon.[4] Inspired by accounts of the thermally promoted isomerization of allenic ketones to furans under the conditions of flash vacuum thermolysis,[5] as well as Marshall's seminal finding that such transformations may be catalyzed by Rh(I) or Ag(I) salts,[6,7] a convergent method for the in situ generation and isomerization of allenic carbonyl compounds to furans under metal-free conditions was sought. Here, we report that exposure of γ-acyloxy butynoates to stoichiometric quantities of triarylphosphine results in reductive condensation to afford substituted furans, by way of allenic ester intermediates.[8,9] As γ-acyloxy butynoates are readily obtained through condensation of ethyl propiolate with aldehydes followed by acylation, this method represents a powerful diversity oriented protocol for the convergent construction of substituted furans.

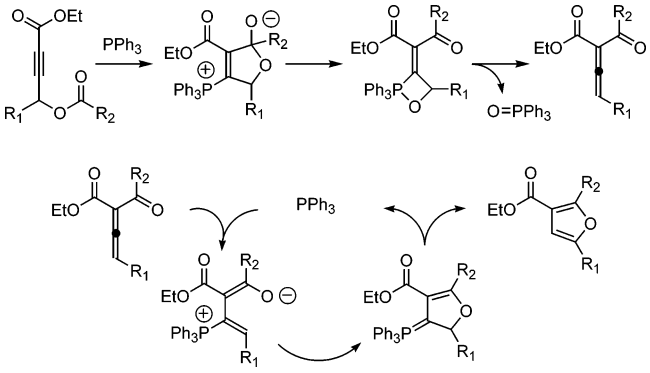


It was postulated that exposure of γ-acyloxy butynoates to stoichiometric quantities of triphenylphosphine would result in tandem conjugate addition−acyl substitution to afford betaine intermediates, which upon extrusion of triphenylphosphine oxide would produce allenic esters. The facile thermal and transition metal-catalyzed isomerization of allenic carbonyl compounds to furans suggests the feasibility of in situ transformation of the allenic ester to the corresponding furan under the conditions of nucleophilic catalysis (Scheme 1).

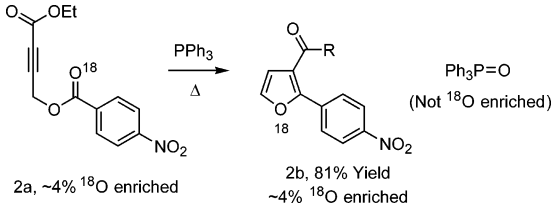
To assess the feasibility of the proposed transformation, the intramolecular reductive condensation the propargylic *p*-nitrobenzoate **2a** was explored. Gratifyingly, through an assay of diverse reactions conditions, it was eventually found that exposure of **2a** to triphenylphosphine (120 mol %) in ethyl acetate solvent at 110 °C in a sealed tube enables formation of the 2,3-disubstituted furan **2b** in 81% isolated yield as a single isomer, as corroborated by single-crystal X-ray diffraction analysis.

Under these optimized conditions, the phosphine-mediated reductive condensation of γ-acyloxy butynoates was investigated. As demonstrated by the intramolecular reductive condensation of propargylic esters **1a**, **2a**, and **4a**, furan formation proceeds most efficiently for substrates that embody increasingly electron-deficient γ-acyloxy moieties (Table 1, entries 1−3). In addition to acetylenic esters, the acetylenic ketone **3a** also participates in the reductive condensation. As illustrated by the intramolecular reductive condensation of substrates **5a**−**8a**, haloaroyl- and heteroaroyl-substituted propargylic esters provide the corresponding furans **5b**−**8b** in good yield (Table 1, entries 4−7). Propargylic esters **9a**, **10a**, and **11a**, derived from oxalic acid, fumaric acid, and crotonic acid, are also viable substrates (Table 1, entries 8−10). Access to 2,4-disubstituted furans is achieved through the reductive condensation of formic acid esters **12a** and **13a** (Table 1, entries 11 and 12). Finally, as demonstrated by the condensation of **14a**−**16a**, trisubstituted furans may be obtained through this method (Table 1, entries 13−15). In general, for highly electrophilic γ-acyloxy partners as represented by substrates **6a**, **11a**, and **16a**, reductive condensation proceeds most efficiently at ambient temperature, and in the former two cases use of a sterically more demanding triarylphosphine, tri-*m*-tolylphosphine, was required. Direct exposure of simple mono-activated allenic esters to the reaction conditions does not result in furan formation, presumably because of internal coordination of the nascent enolate oxygen in the form of the oxaphospholene.[10]

Scheme 1. Postulated Mechanism for Phosphine-Mediated Reductive Condensation of γ-Acyloxy



Scheme 2. Isotopic Labeling Experiment Corroborating the Proposed Mechanism



To corroborate the proposed mechanism, in which the carbonyl oxygen of the γ-acyloxy moiety is retained in the product, exposure of ^{18}O-enriched propargylic ester **2a** to the aforementioned conditions for reductive condensation provides the furan **2b**, which retains the isotopic label. Triphenylphosphine oxide isolated from the

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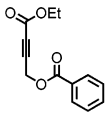
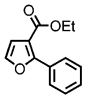
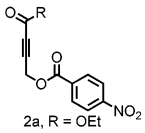
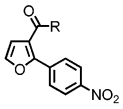
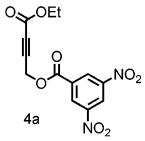
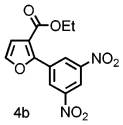
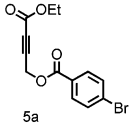
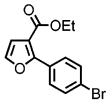
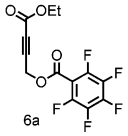
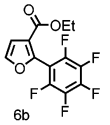
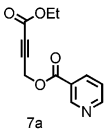
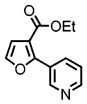
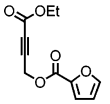
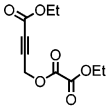
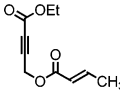
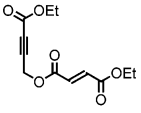
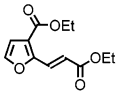
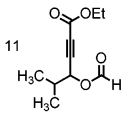
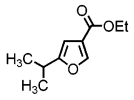
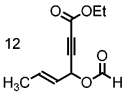
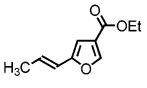
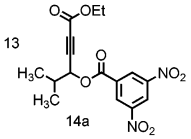
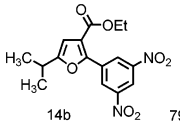
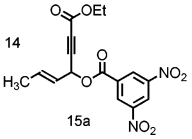
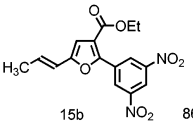
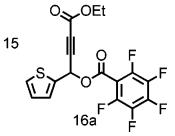
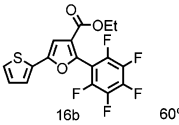
Table 1. Phosphine-Mediated Reductive Condensation of γ-Acyloxy Butynoates To Form Furans[a]

Entry	Substrate	Product	Yield (%)
1	 1a	 1b	72%
2	 2a, R = OEt 3a, R = CH_3	 2b 3b	81% 73%[b]
3	 4a	 4b	91%
4	 5a	 5b	77%
5	 6a	 6b	71%[c]
6	 7a	 7b	68%
7	 8a	 8b	73%
8	 9a	 9b	83%
9	 10a	 10b	83%
10	 11a	 11b	84%[c]
11	 12a	 12b	79%
12	 13a	 13b	71%
13	 14a	 14b	79%
14	 15a	 15b	86%
15	 16a	 16b	60%[b]

[a] Procedure: To a solution of the propargyl ester (100 mol %) in ethyl acetate (0.1 M) was added triphenylphosphine (120 mol %). The reaction vessel was sealed, heated to 110 °C, and allowed to stir until complete consumption of starting material was observed. The reaction mixture was evaporated onto silica gel and subjected to purification by flash chromatography (SiO_2: EtOAc−hexane) to afford the furan. [b] The reaction was conducted at ambient temperature. [c] The reaction was conducted at ambient temperature using (*m*-Tol)$_3$P.

reaction mixture is not ^{18}O-enriched. This result disqualifies mechanisms involving loss of hydroxide followed by alkaline cleavage of the intermediate phosphonium adduct to afford triphenylphosphine oxide (Scheme 2).[11]

In summation, a powerful and mechanistically novel protocol for the convergent three-component assembly of substituted furans has been developed. Future studies will focus on the development of related transformations, and the application of this methodology toward the synthesis of furan-containing natural products.

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Supporting Information Available: Spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). Single-crystal X-ray crystallographic data for compound **2b** (CIF). Mass spectroscopic data corresponding to the isotopic labeling experiment (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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