



One-Pot Synthesis of 2,5-Disubstituted Furans through In Situ Formation of Allenes and Enolization Cascade

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One-pot synthesis of 2,5-disubstituted furans through in-situ formation of allenes and enolization cascade

Yann Bernhard, Joachim Gilbert, Till Bousquet, Audrey Favrelle-Huret, Philippe Zinck, Sylvain Pellegrini, and Lydie Pelinski*^[a]

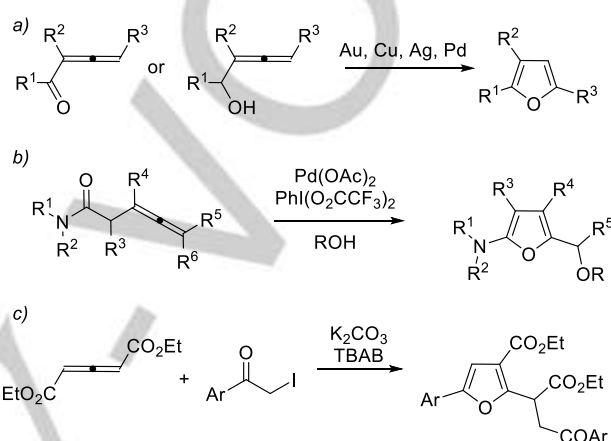
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Abstract: A one-pot synthesis of 2,5-disubstituted furans from γ -ketoacids is reported. In situ formation of allenates by action of chloroformate on carboxylic acid following by enolization of ketone affords to furan derivatives by cyclization. The reaction was extended on a wide scope of ketoacids and phosphonium salts. This methodology was applied on levulinic acid and derivatives, one of the biosourced platform chemicals.

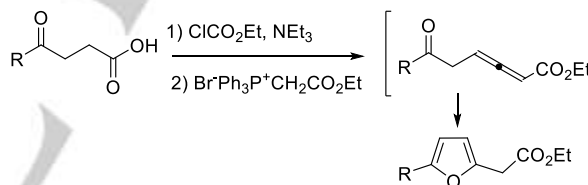
Substituted furans represent an important class of heterocycles, often found in bioactive natural products and pharmacologically active compounds.^[1] As such the attractiveness of furan-containing structures lead to a continuous development of new efficient methods for the synthesis of this heterocycle.^[2] Among the many approaches explored towards their synthesis, homogeneous metal-catalyzed reactions are attractive due to their efficiency and functional group compatibility.^[3] Particularly, a strategy involving cycloisomerization of alkyne using transition-metal catalysts such as rhodium, copper, gold, and palladium complexes is the most studied.^[4] In contrast to metal-mediated processes, organocatalytic approaches to the construction of substituted furan are also described.^[5] Recently, a convenient scandium(III) triflate-catalyzed synthesis of 2,5-disubstituted furans was developed by employing oxiranes with γ -hydroxyketones.^[6]

Allenes are highly valuable synthetic precursors in preparative organic chemistry due to their high reactivity and rich chemistry associated with the two orthogonal carbon-carbon double bonds.^[7] Among the transformations investigated, the transition-metal-catalyzed intramolecular hydrofunctionalization of allenes with heteroatom nucleophiles displays an elegant approach for the synthesis of heterocycles.^[8] Particularly, allenyl ketones or alcohols (Scheme 1, pathway a)^[9] and allenyl amides (Scheme 1, pathway b)^[10] are common starting materials for transition-metal catalyzed furan synthesis.^[11] More recently, multisubstituted furans were obtained by reaction of an allenolate with α -halocarbonyl ketones or dicarbonyl compounds (Scheme 1, pathway c).^[12]

Previous work



This work



Scheme 1. Previous studies and our contribution on furan synthesis

Despite these processes, there is still a requirement to develop new and efficient strategies particularly based on easily accessible starting materials. To this end, we developed a one-pot synthesis of 2,5-disubstituted furans involving an unprecedented formation of allenes as key intermediates (Scheme 1). It is worth noting that the most useful synthesis of allenes consists of a Wittig reaction by reacting a phosphorane or phosphonium salt with activated carboxylic acids such as acid chlorides.^[13] In our study, we propose the possibility to use chloroformates as an alternative to thionyl chloride and oxalyl chloride as activating reagent of carboxylic acid.

We initiated our study with 3-benzoyl propionic acid **1a** as a model substrate. In a typical procedure, the ketoacid **1a** (1 equiv) was first activated by the chloroformate **2** (1 equiv) in the presence of triethylamine (2 equiv) in dichloromethane at 0 °C. After 10 min, the phosphonium salt **3** (0.5 equiv) was added and the mixture was refluxed for 10 h (Table 1). After screening various chloroformates (entries 1-4), we discovered that the desired furan product **4a** was formed in 82% yield in the presence of ethyl chloroformate (entry 2). When the reaction was performed with an equimolar quantity of ketoacid **1a** and phosphonium salt, the yield

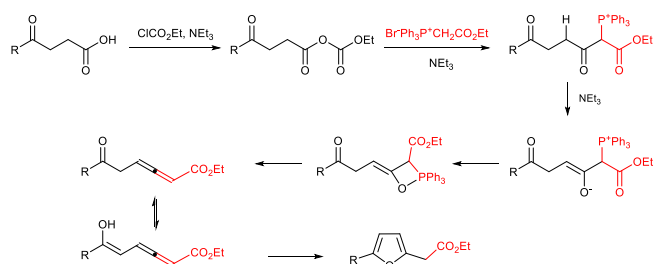
[a] Dr. Y. Bernhard, J. Gilbert, Dr. T. Bousquet, Dr A. Favrelle-Huret, Prof. P. Zinck, Dr. S. Pellegrini, Prof. Dr. L. Pelinski
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dropped from 82 to 62% (Entry 5). Likewise, the reaction did not proceed to completion at room temperature (entry 6). With the exception of replacing the dichloromethane by dimethylformamide (entry 12), the solvents were found to decrease the yields of the transformation of ketoacid (entries 7–11).

The mechanism suggested for this transformation is outlined in Scheme 2. In a first step, the ketoacid reacts with ethyl chloroformate in the presence of triethylamine to form the mixed anhydride carbonate. The latter by action of the phosphonium salt leads to the allene which readily undergoes intramolecular cyclization to furnish the furan derivative. It is worth noting that the assumption of allene formation was confirmed when an additional reaction was set from 3-phenylpropionic acid. In fact, this substrate, which is unable to perform the last cyclization step, allows to isolate the allene in a 60% yield.



Scheme 2. Proposed mechanism

Table 1. Optimisation of the reaction conditions^[a]

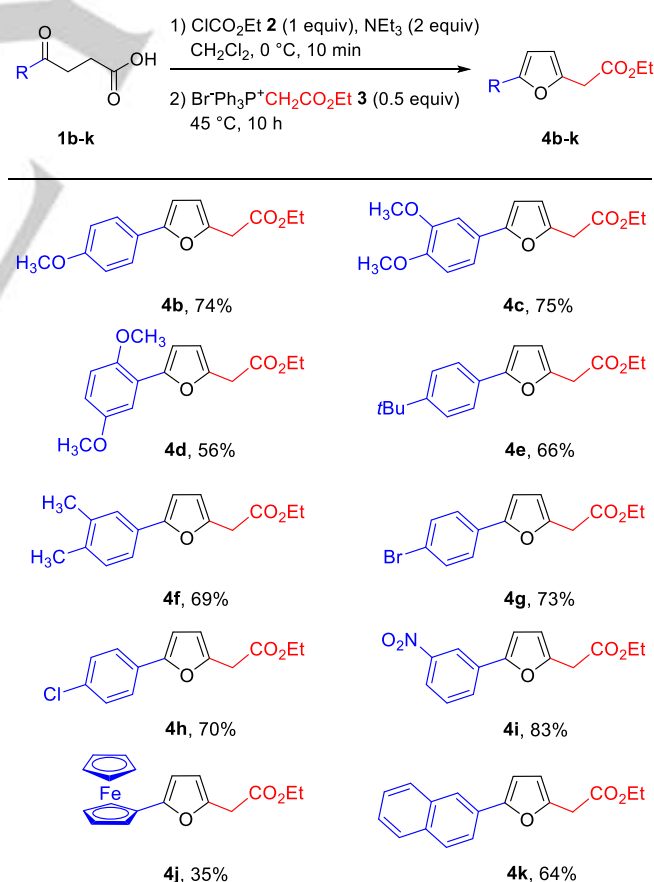
$\text{Ph-C(=O)-CH}_2\text{-C(=O)OH} \xrightarrow[2) \text{ BrP(Ph)}_3^+\text{CH}_2\text{CO}_2\text{Et } \mathbf{3} \text{ (0.5 equiv), 45 }^\circ\text{C, 10 h}]{1) \text{ ClCO}_2\text{R } \mathbf{2} \text{ (1 equiv), NEt}_3 \text{ (2 equiv), solvent, 0 }^\circ\text{C, 10 min}}$			
1a			4a
Entry	2	Solvent	Yield [%] ^[b]
1	ClCO ₂ Me	CH ₂ Cl ₂	68
2	ClCO ₂ Et	CH ₂ Cl ₂	82
3	ClCO ₂ <i>i</i> -Bu	CH ₂ Cl ₂	68
4	ClCO ₂ <i>p</i> -NO ₂ Ph	CH ₂ Cl ₂	0
5 ^[c]	ClCO ₂ Et	CH ₂ Cl ₂	62
6 ^[d]	ClCO ₂ Et	CH ₂ Cl ₂	38
7	ClCO ₂ Et	CHCl ₃	62
8	ClCO ₂ Et	CH ₃ CN	76
9	ClCO ₂ Et	Dioxane	38
10	ClCO ₂ Et	1,2-DCE	70
11	ClCO ₂ Et	Toluene	23
12	ClCO ₂ Et	DMF	79

[a] Reaction conditions: **1a** (1.28 mmol), **2** (1.28 mmol), NEt₃ (300 μL), **3** (0.64 mmol), solvent (10 mL). [b] Isolated yield. [c] In presence of 1.28 mmol of **3**. [d] RT.

With the optimized conditions in hand, we began to investigate the scope of the method. At first, different kinds of substituted benzoylpropionic acids, easily prepared by a Friedel-Crafts reaction between substituted benzene derivatives and succinic anhydride, were evaluated. As shown in Table 2, a broad range of benzoylpropionic acids bearing electron-donating and -withdrawing substituents reacted smoothly with the phosphonium salt **3** in moderate to good yields. The best result of 93% yield was obtained from the meta-nitro substituted substrate. Additionally, electron donating groups such as methoxy, alkyl substituents are compatible with the reaction conditions. However, the lower 56% yield observed for the synthesis of **4d** was likely due to the steric hindrance of the methoxy moiety in the ortho position. The presence of halogens on the benzene ring did not affect the yield (73% for **4g** and 70% for **4h**). The ferrocenyl furan **4j** was obtained in only 35% yield due to heat decomposition.

The scope of the reaction was then extended to various phosphonium salts containing other functions such as ketones or nitrile (Table 3). Apart from furan **6a** (56% yield), the condensation of phosphonium salt **5** led to furan derivatives in good 65–86% yields.

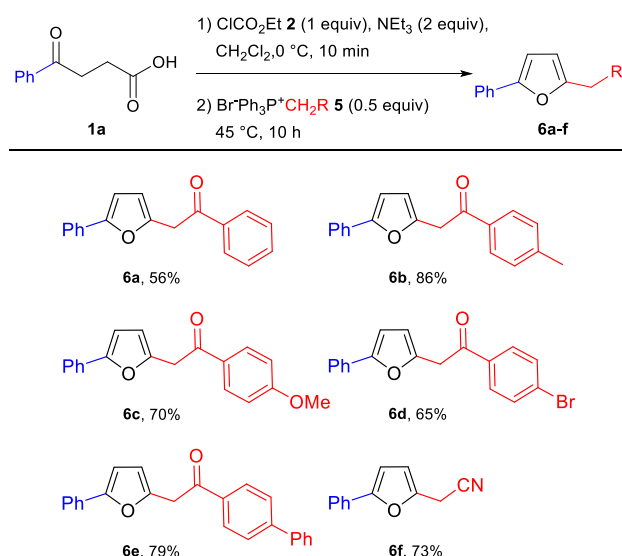
Table 2. Scope of the ketoacid substrates



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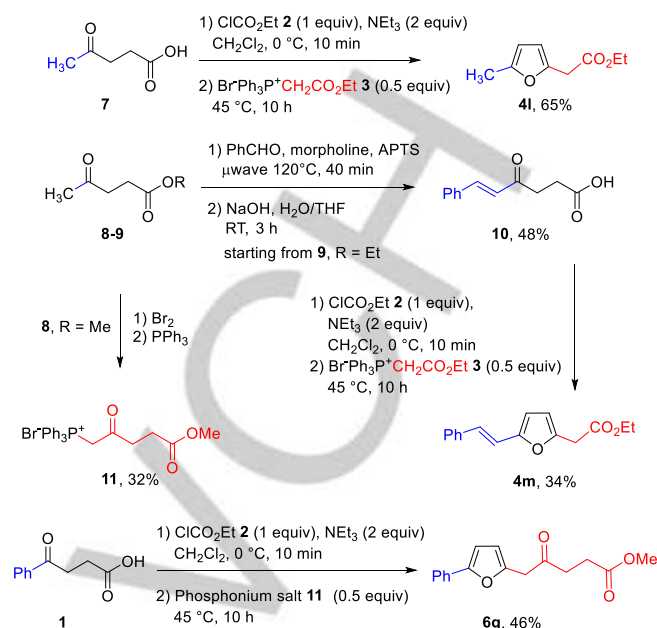
[a] Reaction conditions: **1** (1.28 mmol), **2** (140 μ L), NEt₃ (300 μ L), **3** (0.64 mmol), solvent (10 mL). Yields of the isolated product are given.

Table 3. Scope of the phosphonium salt



[a] Reaction conditions: **1a** (1.28 mmol), **2** (140 μ L), NEt₃ (300 μ L), **5** (0.64 mmol), solvent (10 mL). Yields of the isolated product are given.

Finally, this new synthetic method was performed from the levulinic acid **7**, a promising biosourced platform chemical (Scheme 3).^[14] The furan **4l** was then isolated in a good yield of 65%. Additionally, the ketoacid **10**, obtained by reaction of ethyl levulinate **9** on benzaldehyde following by hydrolysis of ester, led the the furan **4m** with a disappointing yield of 34%. A degradation of the mixture was observed during the synthesis. The reaction of levulinic acid-based phosphonium salt **11** on benzoylpropionic acid **1** led to the furanyl ketoester **6g** in a modest yield of 46%.



Scheme 3. Furan synthesis starting from levulinic acid derivatives

In conclusion, we have developed an efficient method for the synthesis of 2,5-disubstituted furans from γ -ketoacids. The reaction is operationally simple and presents a wide substrate scope. This methodology was further extended to levulinic acid and derivatives in order to valorize a promising biobased platform chemical.

Experimental Section

Typical procedure for the one-pot synthesis of 2,5-disubstituted furans: to ketoacid (1.28 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (2.15 mmol) then ethylchloroformate (1.47 mmol) at 0 °C. After stirring for 10 min, the phosphonium salt (0.64 mmol) was added and the mixture was heated under reflux for 10 h. The mixture was neutralized by aqueous HCl solution 1 M and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified by column chromatography over silica gel (eluent: petroleum ether/diethylether 9/1 then petroleum ether/diethylether 7/3) to give the furan derivatives.

Full experimental details and characterization data are given in the Supporting Information.

Acknowledgements

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Keywords: Furan derivatives • phosphonium salt • allene intermediate • levulinic acid

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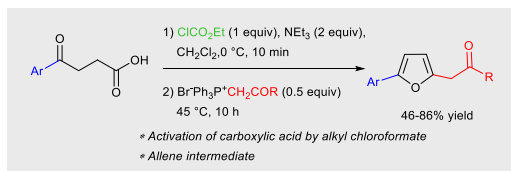
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