

Brønsted Acid-Catalyzed Synthesis of Pyrans *via* a Formal [3 + 3] Cycloaddition

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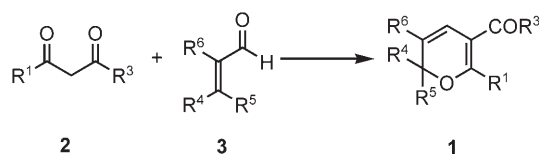


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Abstract: Brønsted acids catalyze the addition of enolizable β -keto esters to α,β -unsaturated aldehydes leading to substituted 2*H*-pyrans in good yields under mild conditions *via* a formal [3 + 3] cycloaddition.

Keywords: cycloaddition; electrocyclic reactions; organocatalysis; oxygen heterocycles; α,β -unsaturated carbonyl compounds

1,3-Dicarbonyl derivatives constitute important synthetic intermediates as they incorporate electrophilic or nucleophilic functionalities.^[1] Rodriguez and colleagues developed anionic methodologies based on the reactivity of stabilized carbanions for the stereoselective synthesis of bicyclo[3.2.1]octanols,^[2a] arylidene-cycloalkanones,^[2b] cycloheptanols,^[2c] and cyclooctane derivatives^[2d] as well as functionalized cyclic enol ethers.^[2e] These 1,3-dicarbonyl compounds, in the presence of α,β -unsaturated aldehydes, can also lead to pyrans and oxodecalins *via* a formal [3 + 3] cycloaddition (Scheme 1).^[3] Such derivatives are common motives and are present in numerous natural products.^[4] Elegant approaches to these intermediates, and their use in synthesis, were described by several groups using either α,β -unsaturated iminium salts as

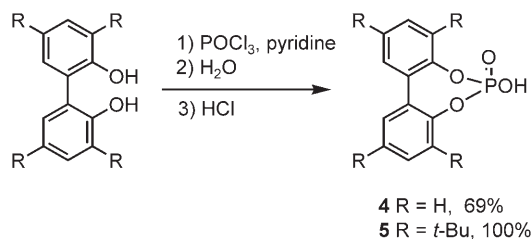


Scheme 1.

activated electrophiles,^[5] Lewis acids as catalysts,^[6] and tandem Stille-oxo-electrocyclization reaction.^[7–10]

Electrophilic activation by small-molecule chiral H-bond donors has emerged as an important tool for enantioselective catalysis, with new applications and developments appearing at a rapidly increasing pace.^[11] Such organocatalysts do not contain any metals and, therefore, are advantageous from environmental perspectives. Compared to Lewis acid, they are less expensive, stable and moisture insensitive. Among the known carbonyl activators, Brønsted acids have recently demonstrated their potential to serve as active catalysts for a variety of synthetically useful reactions in organic chemistry.^[12]

We report here our preliminary results on the synthesis of pyran compounds by a cascade reaction involving diketones **2** and conjugated enals in the presence of a catalytic amount of a Brønsted acid under mild conditions. For this work, the phosphoric acids **4** and **5** were prepared following known procedures,^[13] and isolated in good yields (69% and quantitatively, respectively, Scheme 2).^[14]



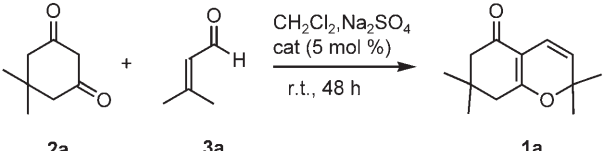
Scheme 2.

3,3-Dimethyl-1,5-cyclohexanedione **2a** has been used as the starting material to synthesize substituted pyrans. A blank reaction carried out at room temper-

ature in dichloromethane overnight with **2a** and 3-methylbut-2-enal **3a**, without any catalyst, did not lead to the desired pyran and only the starting substrates were isolated. We therefore searched for the optimized conditions for this reaction with 3-methyl-2-butenal **3a** in the presence of a catalytic amount of different Brønsted acids (Table 1). As shown in the table, pyran **1a** was isolated in good yield (59 to 73 %) whatever the acid used. However, it is worth mentioning that the phosphoric acids **4** and **5** appeared to be the most efficient as only 5 mol % of them were required to ensure complete conversions and good yields. With the other catalysts, the reaction went to completion with a 15 mol % loading. Using the phosphoric acid **4**, the conversion was slightly lower than those obtained with **5**.

Having established the high potential of this catalytic reaction, we extended it to various α,β -unsaturated carbonyl compounds (Figure 1). Thus 3,3-dimethyl-1,5-cyclohexanedione **2a** reacted with cinnamaldehyde **3b** or nitrocinnamaldehyde **3c** for 48 h to give the pyrans **1b** and **1c** in good yields at room temperature in the presence of 15 mol % of the phosphoric

Table 1. Synthesis of **1a** catalyzed by Brønsted acids.



Catalyst	Conversions [%]	Yields [%]
4 ^[a]	100	70
5 ^[a]	96	73
HBF ₄ ^[b]	96	70
PTSA ^[b]	97	66
PPTS ^[ab]	60	59

^[a] Reaction conditions: 0.75 mmol of aldehyde **3a**, 0.5 mmol of β -diketone **2a**, 0.025 mmol of Brønsted acid (5 mol %) in 5 mL of CH₂Cl₂, 150 mg of Na₂SO₄ (1.05 mmol).

^[b] 15 mol % of catalyst were used.

acid **5**. Alkyl-substituted enals, such as 2-methylbut-2-enal **3d** or citral **3e**, were also reactive and the corresponding pyrans **1d** and **1e** were isolated in the presence of 5 mol % of **5** in 73 % and 95 % yield, respectively.

This protocol proved to be general for the preparation of pyran derivatives and it is worth to mention that the use of Brønsted acids led in high yields to the same 2H-pyrans as when iminium salts^[5] and Lewis acids^[6] but in milder reaction conditions (lower catalyst loading, lower temperature). With 6-methyl-4-hydroxy-2-pyrone or 4-hydroxycoumarin, similar results were obtained after optimization of the reaction conditions as these derivatives are less soluble in dichloromethane at room temperature and led to more sluggish reactions. Thus with alkyl-substituted enals, pyrans **1f–p** (Figure 2) were isolated in good yields in toluene at 60 °C.^[15,16]

In conclusion, we have described a Brønsted acid-catalyzed pyran synthesis from α,β -unsaturated alde-

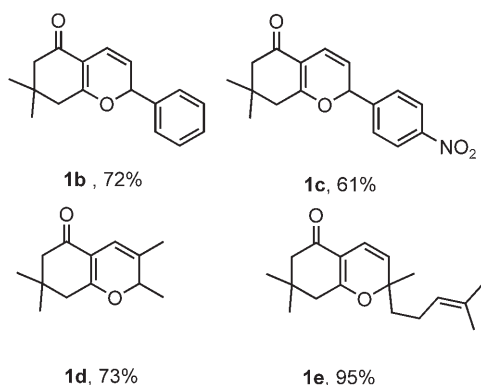


Figure 1.

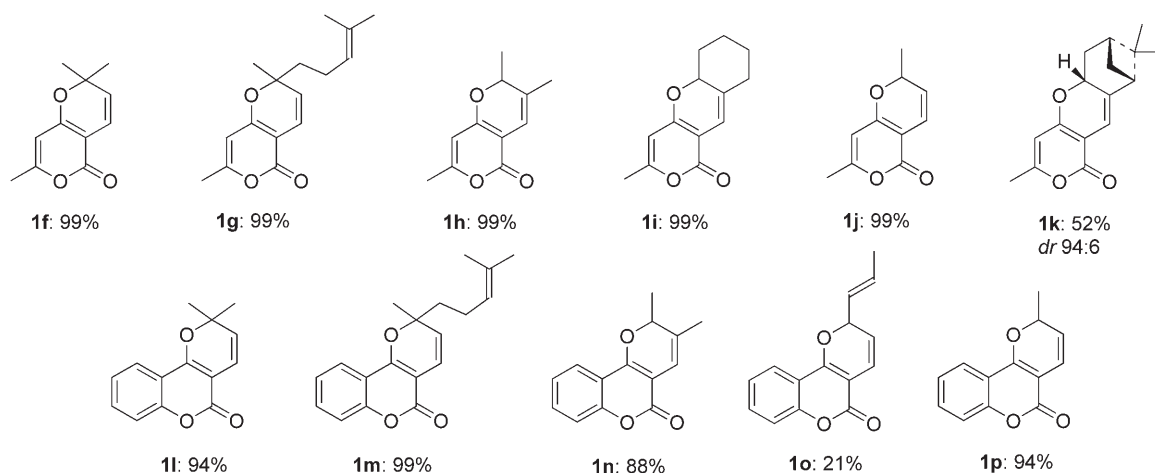


Figure 2.

hydes and 1,3-diketones, 4-hydroxycoumarin or 6-methyl-4-hydroxy-2-pyrone in mild conditions. This simple procedure using stable, moisture insensitive and not expensive catalysts should open new opportunities in organic chemistry and applications in synthesis.

Experimental Section

General Procedure for the Synthesis of the 2H-Pyrans

To previously dried sodium sulfate (150 mg) were successively added under argon, phosphoric acid **4** or **5** (5 mol %), dichloromethane or toluene (10 mL mmol⁻¹), the diketone (1 equiv.) and the unsaturated aldehyde (1.5 equiv.). The solution was stirred at room temperature in dichloromethane or at 60 °C in toluene until completion by TLC analysis. The solution was then filtered through Celite, and concentrated under vacuum. The crude mixture was purified on silica gel by flash chromatography (eluent: heptane/ethyl ether, 9/1).

Supporting Information

Experimental details, NMR spectral characterization data for all compounds are given in the Supporting Information.

Acknowledgements

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- [15] In toluene at 40 °C, the yields were comparable but the reaction times were longer; in CH₂Cl₂, the yields were lower.
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