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HFIP-assisted Brønsted acid catalysed synthesis of furan derivatives

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ABSTRACT

The furan framework is ubiquitous in naturally occurring compounds, and furan-containing structures are also key intermediates to many industrially important chemicals and materials. There have been reports of numerous methods to synthesise furans, however most of them use transition metal catalysts or Brønsted acid catalysts under harsh conditions. This work describes the development of a new non-metal Brønsted acid catalytic method for the synthesis of 2-aryl-3-carboxylate ester furans and 2,3-diaryl furans from ynone substrates. The method was shown to be efficient under very mild reaction conditions with up to 94% product yields.

Keywords: Brønsted acid catalysis, catalysis, cyclization reaction, furan, HFIP, hydrogen-bonding, metal-free, solvent effect.

Introduction

The furan framework is ubiquitous in naturally occurring compounds,[1] and furan-containing structures are also key intermediates to many industrially important chemicals and materials.[2] Many furan derivatives exhibit bioactivity and have been used as anti-infective, anti-tumour, cardiovascular and anti-inflammatory agents. Examples of furan-containing pharmaceuticals that are currently on the market include Nitrofurantoin®, an antibiotic, and Amiodarone®, a potent antiarrhythmic (Fig. 1).[3] Industrially, furan derivatives can also be found in a range of pesticides, and they can be polymerised to form chemically resistant resins and lacquers. An example of a binder resin which has recently been developed is the polyfurfuryl alcohol resin (Fig. 1), which can be made from biomass, a renewable source.[4]

Although there are many naturally occurring furan compounds, it is important to develop new synthetic methods to access useful naturally occurring furans on a larger scale, as well as synthetic structural analogues. The development of new methods may also allow the design and synthesis of specific furan frameworks with suitable structural features for niche applications. Classical approaches to furan synthesis include Paal–Knorr and Feist–Bénary synthesis (Fig. 2*a*), and they are still being used in modern synthetic chemistry. The main disadvantage of the Paal–Knorr synthesis of furans is the difficulty of synthesising reaction substrates,[5] while the key issue with Feist–Bénary is reaction efficiency. An increasingly popular approach to synthesising furan derivatives in the past decade is the intramolecular cyclisation of ynone substrates, which have ketone and alkyne functionalities at 1,4-positions. This 4-pentyne-1-one backbone structure can cyclise intramolecularly through a 5-*exo*-*dig* manner to form substituted furans with functionalisation possible on the C2, C3 and C5 positions (Fig. 2*b*). This reaction does not occur spontaneously, but a wide range of catalysts can be used to facilitate the reaction via different mechanisms. In recent years, numerous metal-based Lewis acid catalysts have been used to promote this reaction. Most notable catalysts include $FeCl_3$ as reported by Golonka and Schindler[6] and $Bi(OTf)_3$ as developed by Chang and co-workers.[7,8] However, these methods associate with the issue of trace metal impurities after product purification, while non-metal catalysts have been rarely used.[9,10] The development of

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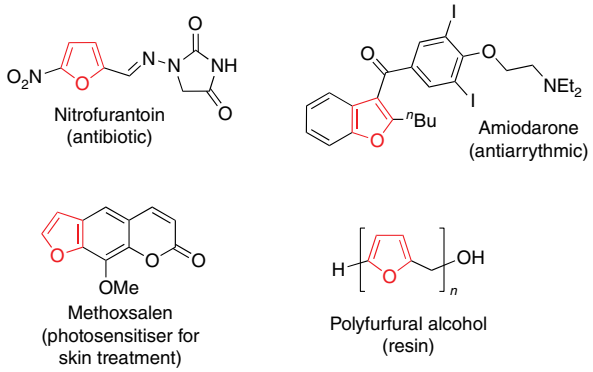


Fig. 1. Some examples of valuable furan-containing compounds.

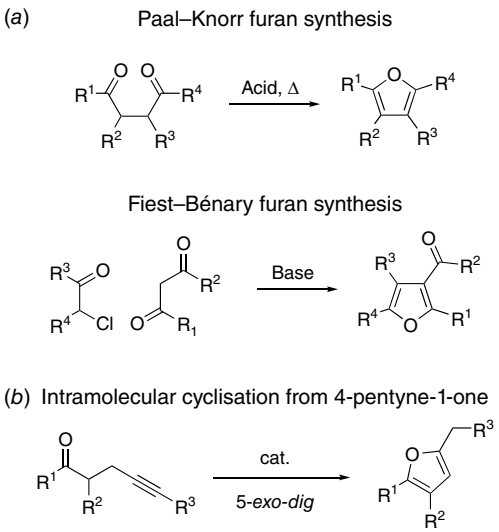


Fig. 2. Paal–Knorr and Feist–Bénary furan synthesis.

novel synthetic methods to access furans using organic catalytic systems is thus attractive as they may be able to overcome the limitations of established pathways.

Results and discussion

Inspired by our previous work on metal-free cyclisation reactions[9,11–15] especially the I_2-catalysed furan synthesis[9] and the HFIP-assisted carbonyl-olefin metathesis reaction,[14] we decided to investigate the catalytic activity of *para*-toluenesulfonic acid **1** (pTSA)/1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in the promotion of the intramolecular cyclisation reactions of ynones to form furan derivatives. pTSA, also denoted as TsOH, is a relatively strong organic Brønsted acid that is commonly used in synthetic laboratories due to its excellent solubility in polar solvents and bench-stability, as it is a solid at room temperature.[16,17] These properties, in addition to its inexpensive cost, ready availability and low toxicity, allow pTSA to be a good homogenous reaction promoter in organic synthesis.

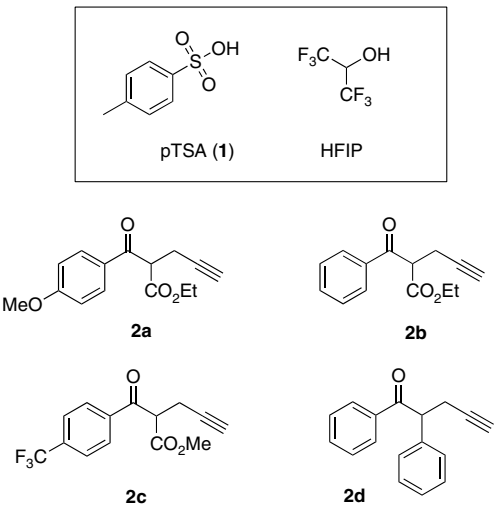


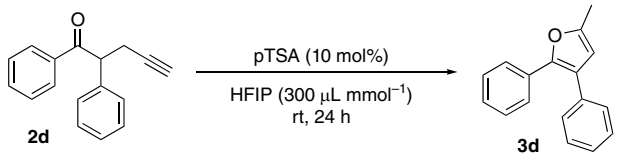
Fig. 3. pTSA/HFIP catalytic system and model substrates.

HFIP is a highly polar solvent capable of hydrogen bonding and cation stabilisation with low nucleophilicity.[18] It has a low boiling point of 59°C, which allows it to be easily removed under reduced pressure or through distillation, where it can potentially be reused. HFIP has become increasingly popular in organic synthesis as it can increase reaction rate and product yield and promote otherwise unfavourable reactions due to the substrate's electronic effects.[19] It is often used in conjunction with Lewis or Brønsted acid catalysts, and works that explore the mechanism of the reaction suggest that the HFIP activates the catalyst by creating hydrogen bonds with the catalyst and substrate (Fig. 3).[19]

Initial screening reactions on four model substrates **2a–d** with pTSA in more conventional lab solvents such as toluene, THF, MeCN, DCM or DCE were quickly confirmed to be ineffective, which was consistent with the literature.[6] Gratifyingly, our test reactions with the pTSA/HFIP catalytic system showed > 50% conversion for all four substrates when heated. These reaction mixtures were relatively clean with only trace amounts of unwanted by-products. The reaction was subsequently optimised using **2d** as the model substrate and HFIP as solvent. This substrate was chosen as it was easy to synthesise in large batches, unlike substrates **2a–c** (see the Supporting Information for details). After an extensive optimisation study, we concluded that the reaction was most efficient with 10 mol% of pTSA catalyst in 300 μL HFIP per mmol of substrate, or 3.3 M concentration, at ambient temperature with reaction time ~24 h. Some notable variations from optimal conditions are presented in Table 1, while the full optimisation study can be seen in pages S3–S7 of the Supporting Information.

Having the optimal conditions in hand, we applied these to a range of ynone substrates. Most of them worked well to form furan products using our newly developed protocol (Scheme 1). Product purification was also straightforward

Table 1. Optimisation study with substrate **2d**.[A]



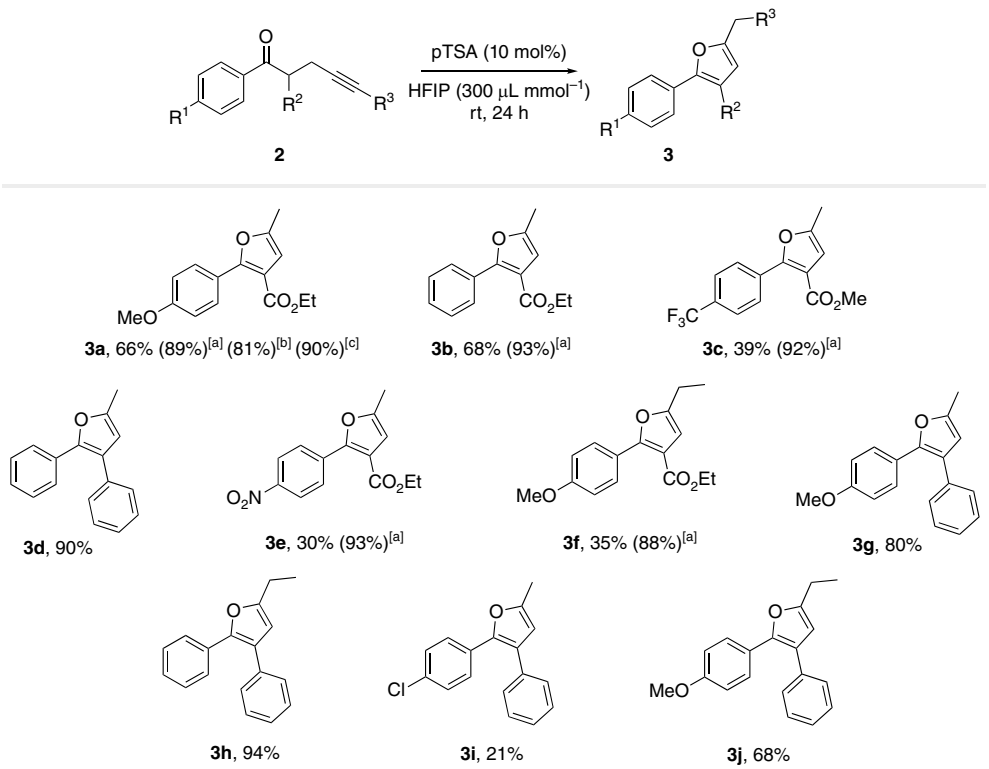
Entry	Variations from optimal conditions	Yield of 3d[B] (%)
1	None	100
2	TfOH instead of pTSA	42
3	CF_3CO_2H instead of pTSA	n.p.
4	HBF_4 instead of pTSA	53
5	Toluene instead of HFIP	n.p.
6	DCE instead of HFIP	n.p.
7	THF instead of HFIP	n.p.
8	MeCN instead of HFIP	n.p.
9	HFIP 500 μL instead of 60 μL	77
10	HFIP 200 μL instead of 60 μL	95
11	HFIP 40 μL instead of 60 μL	96

[A]Reaction conditions unless otherwise stated: **2d** (0.2 mmol) with catalyst (10 mol%) in HFIP (60 μL), rt, 24 h.
[B]Yields of **3d** were calculated from ^{1}H NMR spectra of the crude product mixture with mesitylene as an internal standard. n.p., no product. See pages S3–S7 of the Supporting Information for further details.

as no reaction workup was required and reaction mixtures were generally simple with minimal by-product formation. The reaction substrates were well separated from the products by column chromatography due to the difference in hydrogen bonding capabilities of the carbonyl and furan functionalities, as well as the lack of enolisation in the products.

Some more challenging substrates required modification of the optimal conditions to obtain better efficiencies. Reaction yields were found to be relatively low for α-carboxyloxy ynone substrates as optimisation was actually completed on an α-aryl ynone substrate (**2d**). This decrease in yield was caused by low substrate-to-product conversion, and therefore we found that increasing the reaction time or temperature would lead to an increased reaction yield. Indeed, the variation of reaction conditions with substrate **2a** showed that **3a** could be obtained in 90% yield by either leaving the reaction mixture for 5 days at room temperature or by heating the reaction mixture to 50°C for 24 h. The reaction was therefore repeated for other α-carboxyl ynone substrates at 50°C with excellent results.

Our product yields were comparable to yields from established methods in the literature, as Golonka and Schindler achieved yields of 94 and 95% for **3a** and **3b** respectively in their work.[6] Their reaction conditions were similar, with 10 mol% $FeCl_3$ catalyst and 48 h at room temperature.



Scheme 1. The substrate scope. Yields are of isolated products. Yields in parentheses were calculated using NMR spectra from reactions carried out on a 0.2 mmol scale [a] at 50°C, [b] at room temperature for 3 days and [c] at room temperature for 5 days.

Similarly, our yields for 2,3-diaryl furans were comparable to yields achieved by Chan *et al.* as they produced **3d** with 88% yield.[7] Unfortunately most of the other substrates they used were substituted on the C3 aryl so further product yield comparisons were not possible.

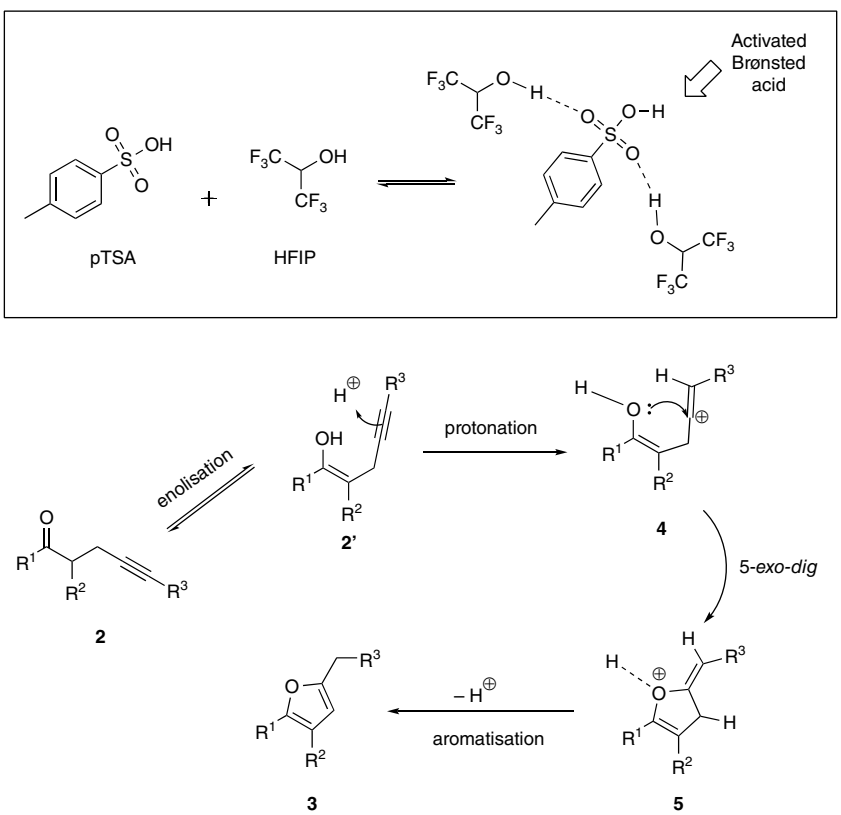
The comparison of room temperature α-carboxyloxy product yields (**3a–c**, **e**, **f**) highlight the impact of the R^1 substituent. Yields of substrates with electron donating or neutral groups (**3a**: 66%, **3b**: 68%) were consistently higher than those with electron withdrawing groups (**3c**: 39%, **3e**: 30%). This was also evident in α-aryl substrates (**3d**: 90%, **3g**: 80% vs **3i**: 21%). From this, we can propose that either electron withdrawing moieties deactivated the substrate which led to higher activation barriers as mentioned before, or the mechanism proceeds through a carbocation intermediate that is more stabilised with neutral/electron-donating substituents. The second theory is plausible as the carbocation intermediate was well documented in the literature.

Similarly, as mentioned before, comparisons of room temperature yields of **3a**/**3g**, **3b**/**3d**, and **3f**/**3j** which differ only by the R^2 group show that substrates with the phenyl group have significantly higher yields than substrates with the ester group (14–33% difference). From this, we can see that the electronic character of R^1 and R^2 groups impact reaction yields in a similar manner, and therefore, they may be acting on the same part of the molecule. Alternatively, this could be justified individually as the phenyl group may be more useful in stabilising the intermediate than the ester group, as it is available for bonding interactions, which may occur within or between aryl structures on molecules. The rigidity of the phenyl ring may also assist product formation more compared to the ester as the ester may have to expend energy to move into a favourable conformation.

Based on all these insights, and mechanistic discussions provided in the literature for similar acid-catalysed reactions,[9,14] a hypothesised reaction mechanism is proposed in Scheme 2. In this hypothesised mechanism, HFIP acts as a highly ionising and strong hydrogen-bonding solvent which would coordinate to pTSA and render it a much stronger Brønsted acid. At the same time, it favours the enol form **2′** of the substrate. Protonation of **2′** leads to the formation of carbocation intermediate **4**, which cyclises in 5-*exo-dig* fashion to give intermediate **5**. Aromatisation of **5**, most likely via a proton transfer step, affords product **3**.

Conclusion

We have developed a new metal-free catalytic system with pTSA in HFIP which can efficiently cyclise ynone substrates to access a range of 2-aryl-3-carboxylate ester furans and 2,3-diaryl furans with high yields of up to 94%. The reaction was also shown to be viable under ambient conditions for electron rich 2,3-diaryl furans.



Scheme 2. Proposed mechanism for the pTSA/HFIP promoted 5-*exo-dig* cyclisation.

Supplementary material

The Supporting Information is available free of charge and includes experimental details and spectroscopic data for all products. Supplementary material is available online.

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Data availability. The data that support this study are available in the article and accompanying online supplementary material.

Conflicts of interest. There is no conflict of interest to declare.

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Author contributions. T. V. N. conceived the ideas and designed the project. B. P. carried out all experimental work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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