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Metal-Free and Sustainable Strategies in the Synthesis of Substituted Furans: A Contemporary Review

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Abstract

Furans and their derivatives play an important role in synthetic organic chemistry and biological chemistry, and they serve as key structural units in numerous natural products. In recent times, environmentally benign synthetic processes have emerged as a vital strategy for the production of fine organic chemicals. This review article summarises recent advances in various transition metal-free, sustainable synthetic methodologies for the synthesis of substituted furans. The focus is placed on literature reports published during the past five years (2020–2025). Various synthetically important methodologies—such as catalytic methods, cycloaddition reactions, and multicomponent reactions—used to prepare substituted furan scaffolds have been critically reviewed. Particular emphasis has been placed on metal-free methods that adhere to the principles of Green Chemistry.

Keywords: *Biological Activities; Cycloaddition Reaction; Green Chemistry; Metal-Free Synthesis; Multicomponent Reaction; Substituted Furans*

Introduction

Furan and its derivatives are heterocyclic organic compounds featuring a five-membered aromatic ring composed of four carbon atoms and one oxygen atom. Furan itself is a colourless, highly volatile, and flammable liquid with a boiling point close to room temperature (Joule & Mills, 2010). It exhibits aromatic properties (Resonance energy= 16 kcal/mol or 67 kJ/mol) due to the delocalisation of π-electrons within the ring (Figure 1).

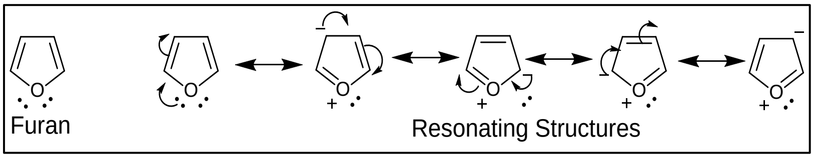


Figure 1: Furan and its resonating structures

It is an important class of organic compound because it acts as a key structural unit in numerous natural products and also has been found to exhibit several biological activities, such as anti-inflammatory, anticancer, antioxidant, antifungal, antibacterial, antispasmodic and herbicidal activities (Saeid, Al-sayed & Bader, 2023). Compounds comprising the furan ring are biologically active and are existent in a number of pharmaceutical products (Figure 2).

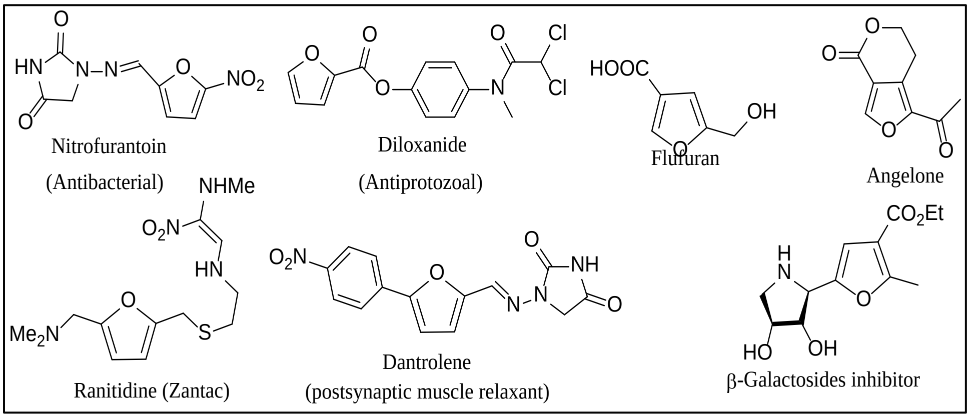


Figure 2: Biologically active furans

Furan rings act as unique synthetic intermediates because of the low resonance energy value of the furan scaffold (Gubina & Kharchenko, 1995). They undergo a number of synthetically useful transformations, such as addition reactions, metalations, cycloadditions, Ring-opening reactions, and electrophilic substitutions (Eicher, Hauptmann & Speicher, 2003).

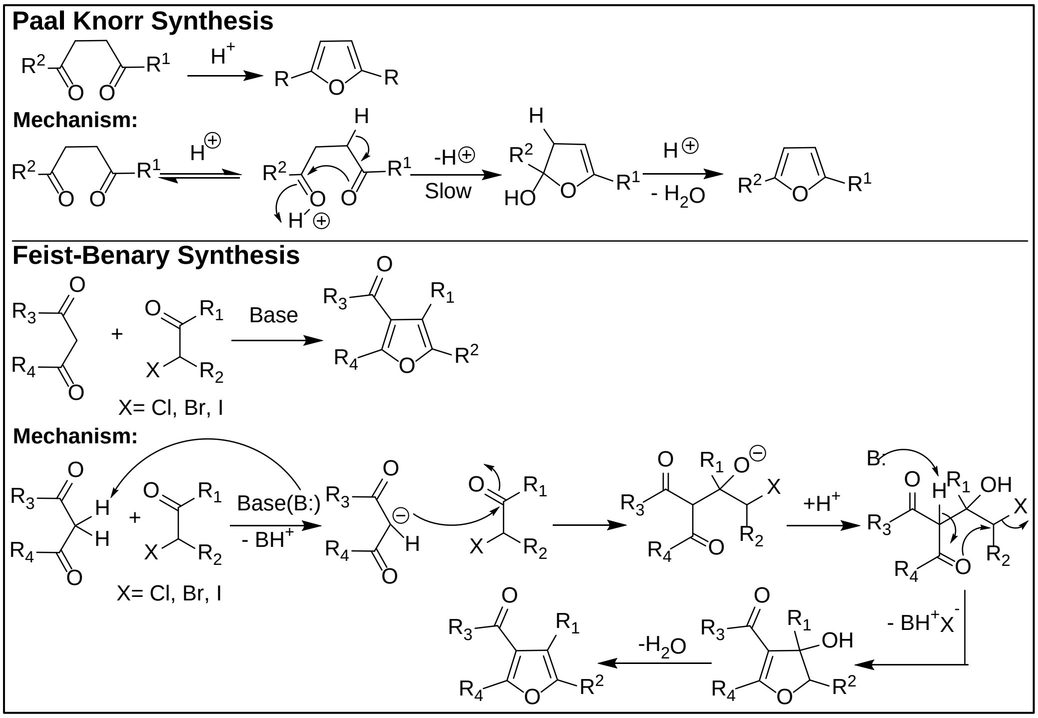
Due to the wide range of biological and synthetic importance, various synthetic methodologies have been developed for the synthesis of the furan moiety over the years (Deepthi, Babu & Balachandran, 2019). This book chapter discusses the metal-free, green, and sustainable synthetic methodologies that have been explored for the construction of substituted furan scaffolds over the past five years (2020–2025).

Literature Review

Many synthetic approaches have been followed for the construction of furan scaffolds. The most classic synthetic route to achieve poly-substituted furan is Paal-Knorr synthesis, which is basically an acid-catalysed cyclisation of 1,4-dicarbonyl compounds (Khaghaninejad & Heravi, 2014; Li, 2009) (Scheme 1).

Another classical synthetic method is the Feist–Benary synthesis which is an organic reaction between *β*-dicarbonyl compounds and *α*-halo ketones which leads to substituted furan compounds. Contrary to the Paal-Knorr synthesis, this cyclocondensation reaction is catalssed by a base (Scheme 1) (Peng *et al.,* 2016).

Recently, a diverse array of advanced methodologies has been developed for the construction of furan scaffolds, including (a) transition metal-catalysed construction of furan skeletons (Gulevich *et al.,* 2013) (b) direct functionalisation of the furan core to achieve substituted furan moieties (Karlinskii & Ananikov, 2021) (c) catalytic methods for the preparation of substituted furans from sugar and biomass (Romo *et al.,* 2018) facilitating the rapid and efficient synthesis of structurally diverse furan frameworks.



Scheme 1: Paal-Knorr and Feist-Benary Synthesis of Poly-substituted Furan

Although these methods have demonstrated efficiency in synthesising substituted furan derivatives, they exhibit certain limitations, including the reliance on costly metal catalysts, the use of environmentally hazardous solvents, and the requirement for harsh reaction conditions. Consequently, there is a strong impetus to develop straightforward, cost-effective, and, most importantly, metal-free green and sustainable methodologies for the synthesis of densely functionalised furan derivatives from readily available starting material. This book chapter will primarily focus on metal-free, sustainable, and environmentally benign synthetic strategies for the construction of substituted furans, as highlighted in recent advancements.

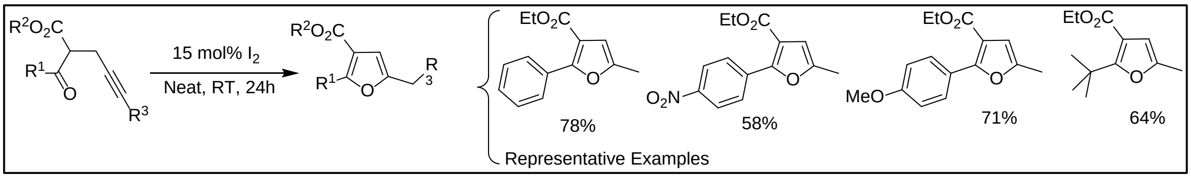
Discussion

A recent literature survey covering the last five years (2020–2025) reveals that numerous efforts have been made to develop non-metallic synthetic routes for the construction of poly-substituted furan scaffolds. The synthetic reports have been documented as follows:

Synthesis of Substituted Furans *via* Various Metal-Free Catalytic Methods:

Iodine Catalysed Synthesis of Substituted Furan:

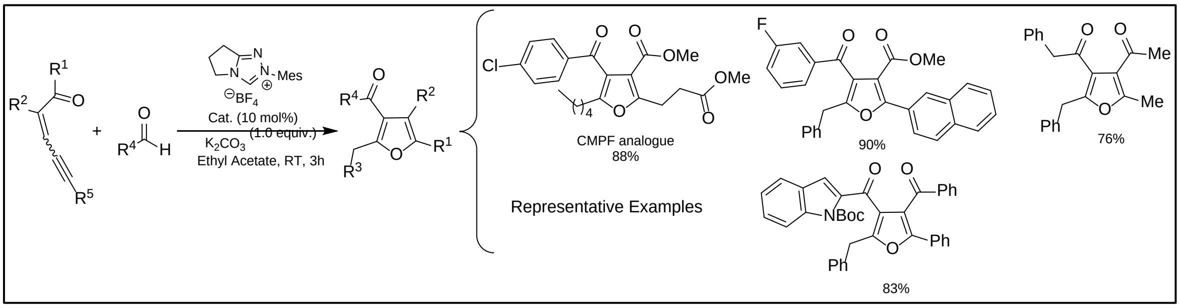
Pace *et al.* (2021) introduced an efficient and practical approach for synthesising 3-carboxy-2,5-disubstituted furans. Their method utilises *α*-propargyl-*β*-ketoester substrates and employs molecular iodine as a catalyst under mild conditions. This protocol accommodates a wide variety of functional groups and provides an environmentally friendly alternative to existing methods for obtaining furan derivatives. After conducting DFT (Density Functional Theory) calculations, the authors determined that the reaction mechanism is complex and may involve multiple competing pathways occurring simultaneously (Scheme-2).



Scheme 2: Synthesis of 3-carboxy-2,5-disubstituted Furans

NHC Catalysed Synthesis of Substituted Furan:

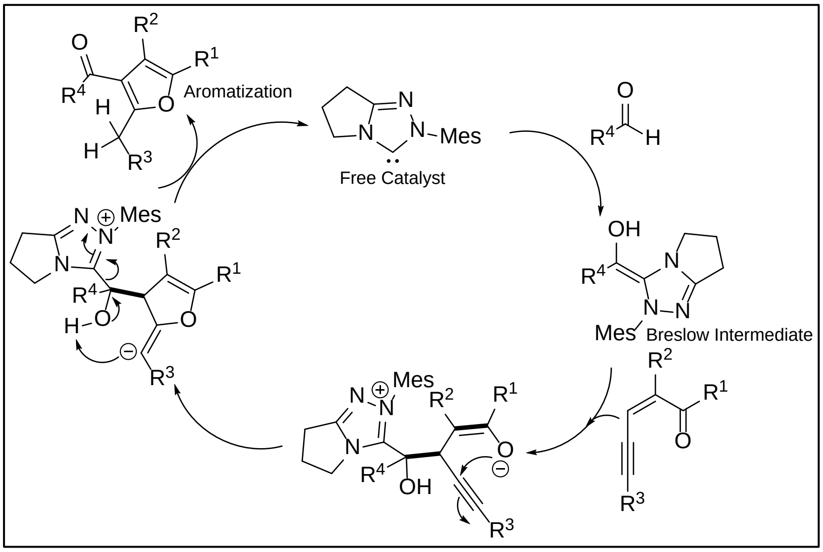
A recent study by the research group of Wang (2024) presents an efficient and selective approach for synthesising highly substituted furans. They have demonstrated an innovative *N*-heterocyclic carbene (NHC)-catalysed strategy that enables the cross-coupling and cyclisation of readily available ynenones with various aldehydes (Scheme 3). This method is characterised by high atom economy, mild reaction conditions, broad substrate compatibility, and excellent functional group tolerance.



Scheme 3: Synthesis of Tetra-Substituted Furans from Enynone Catalysed by NHCs

The proposed reaction mechanism, illustrated in Scheme 4, begins with the base activating the catalyst. This active catalyst then interacts with the aldehyde, leading to the Breslow intermediate.

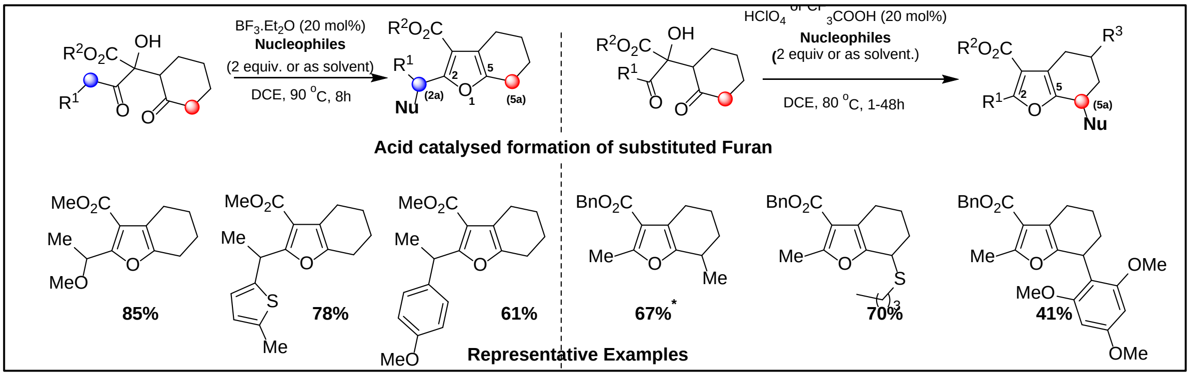
Subsequently, the Breslow intermediate undergoes a reaction with the alkenyl group of enynone, generating intermediate I. This intermediate then proceeds through a 5-exo-dig cyclisation, yielding intermediate II. Finally, the aromatisation step results in the desired product (Scheme 4).



Scheme 4: Plausible Mechanism of NHC Catalysed Tetra-substituted Furans Formation

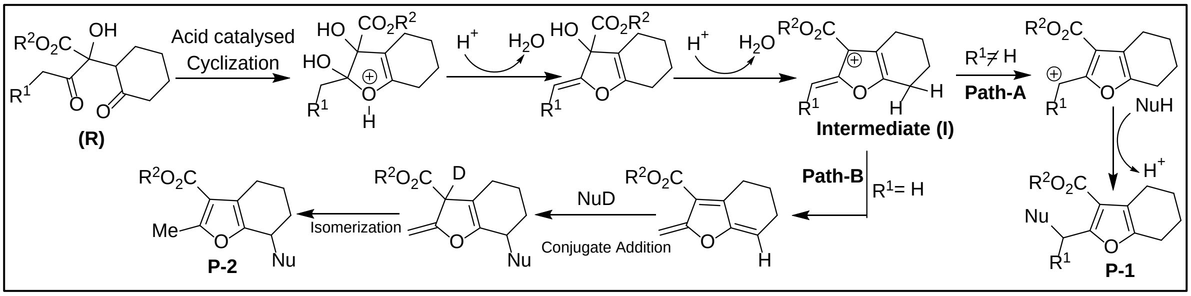
Acid Catalysed Synthesis of Substituted Furan:

Liu’s research group (2021) developed a novel divergent approach for synthesising substituted furan derivatives from 2-hydroxy-1,4-diones *via* an acid-catalysed method. The reaction enables selective functionalisation at either the 2a or 5a position of the resulting product, determined by the structure of the starting material (Scheme 5).



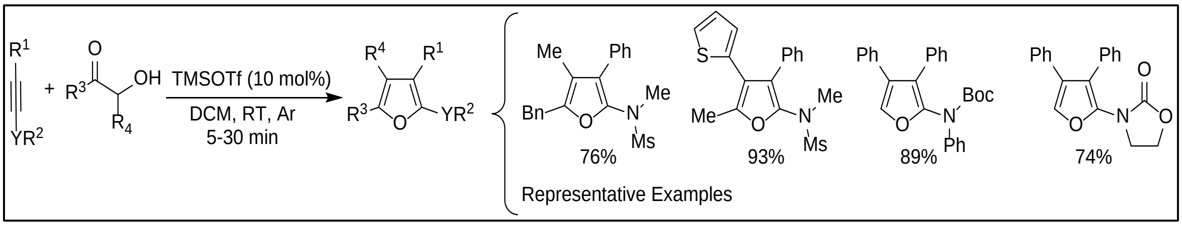
Scheme 5: Synthesis of Substituted Furan by Cascade Reactions

The authors proposed a plausible reaction mechanism that accounts for the formation of different products based on the structure of the starting materials (Scheme 6). When the R^1 group is a hydrogen atom, a 1,4-hydrogen elimination proceeds *via* the Path-B mechanism, generating a 1,3,5-triene intermediate. A subsequent 1,6-conjugate addition by a nucleophile, followed by isomerisation, leads to the formation of the product P-2. In contrast, when R^1 is an alkyl group, the reaction follows Path-A, involving a carbocation rearrangement that is quickly intercepted by a nucleophile through a Friedel–Crafts-type reaction, yielding the functionalised product P-1 (Scheme 6).



Scheme 6: Proposed Reaction Mechanism

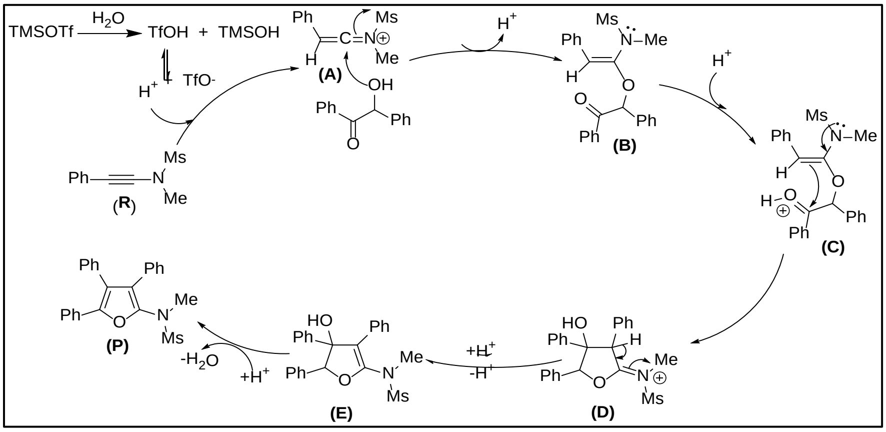
Chen and colleagues (2021) developed a metal-free method for synthesising poly-substituted furans through a TMSOTf-catalysed formal [3+2] cycloaddition between electron-rich alkynes and *α*-hydroxy ketones. This approach is an atom economic method that generates water as the primary by-product (Scheme 7).



Scheme 7: TMSOTf-catalysed Synthesis of Substituted Furans

Mechanistic investigations indicate that the reaction likely follows an acid-catalysed sequence involving syn-addition, cyclisation, and aromatisation steps (Scheme-8). In the initial stage, TMSOTf may react with trace water present in the system to generate TfOH. The resulting TfOH then activates the ynamide (R), leading to the formation of a reactive keteniminium ion intermediate (A). This intermediate is intercepted by the hydroxyl group of benzoin, resulting in the formation of the enamide intermediate (B).

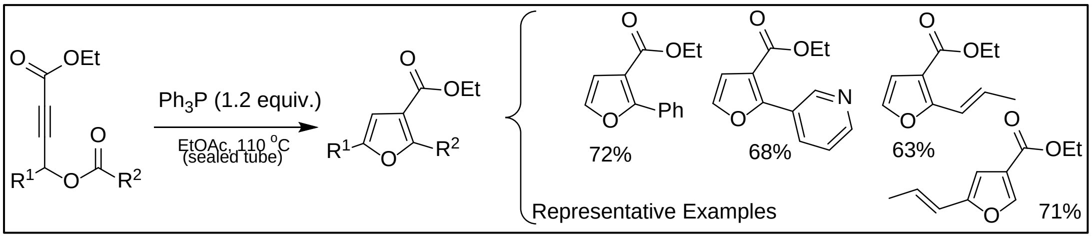
A subsequent intramolecular nucleophilic attack on the acid-activated carbonyl group produces iminium ion (D). This species undergoes enamide–iminium tautomerisation to form another enamide intermediate (E), which then undergoes acid-catalysed dehydration to furnish the final product (P) (Scheme 8).



Scheme 8: Proposed Reaction Mechanism of Furan Synthesis through Acid Catalysis

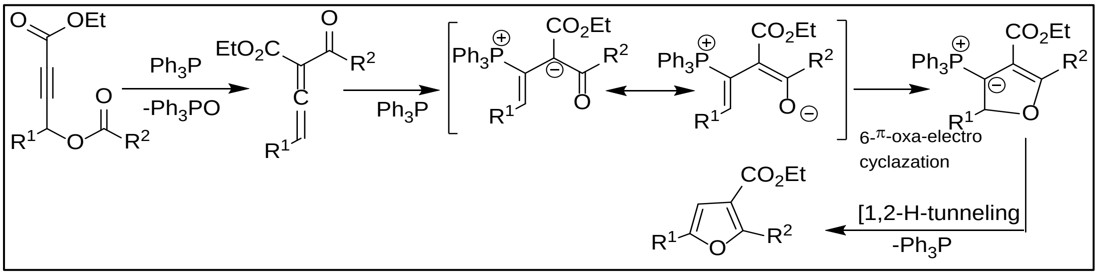
Phosphine Mediated Synthesis of Substituted Furan:

The phosphine-mediated synthesis of substituted furan moieties has been the subject of extensive study for many years (Kuroda, Hanaki & Kawakami, 1999; Wang *et al.,* 2011). In 2004, Jung, Wang and Krische reported phosphine-mediated reductive condensation of *g*-acyloxy butynoates to form furans (Krische furan Synthesis) (Scheme-9).



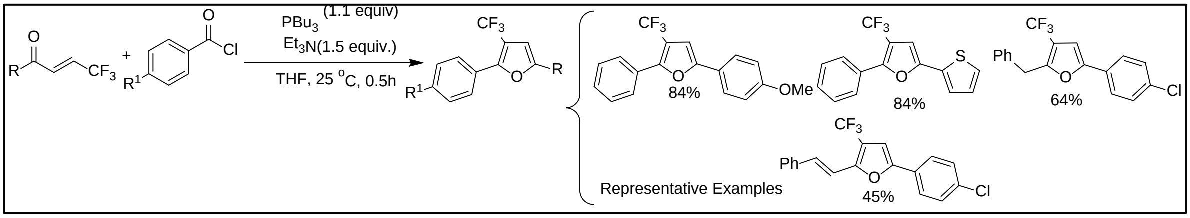
Scheme 9: Krische Furan Synthesis

Very recently, Wang *et al.* (2024) reinvestigated the Krische furan synthesis method. It is accepted that Ph_3P-mediated formation of the acyl allenoate intermediates is a crucial step for this reaction (Scheme-9). The ketene intermediate subsequently undergoes 6*π* oxa-1,5-electrocyclisation catalysed by organophosphine. The final step is a cascading [1, 2]-H shifts followed by eliminative aromatisation to give rise to the substituted furans.



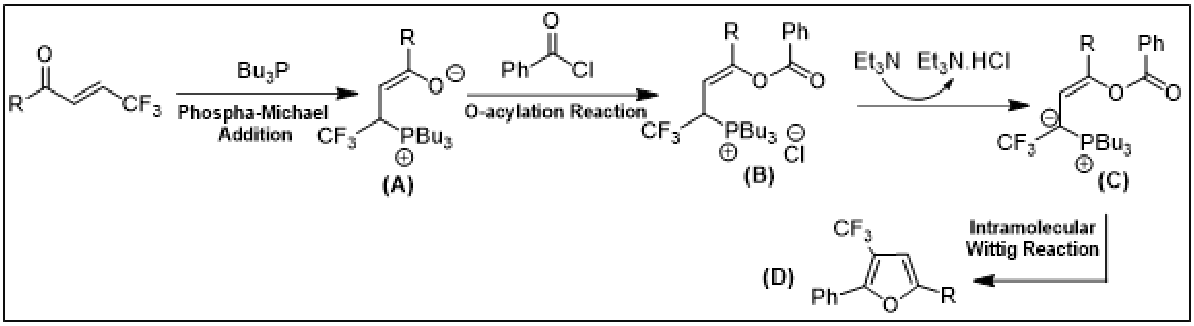
Scheme 10: Mechanistic Pathway of the Krische Furan Synthesis

Recently, Li and Zhou (2020) have effectively developed a highly efficient method involving nucleophilic addition, *O*-acylation, and an intramolecular Wittig reaction of *β*-trifluoromethyl *α,β*-enones, enabling the synthesis of trifluoromethyl-functionalised, multi-substituted furan compounds (Scheme 11).



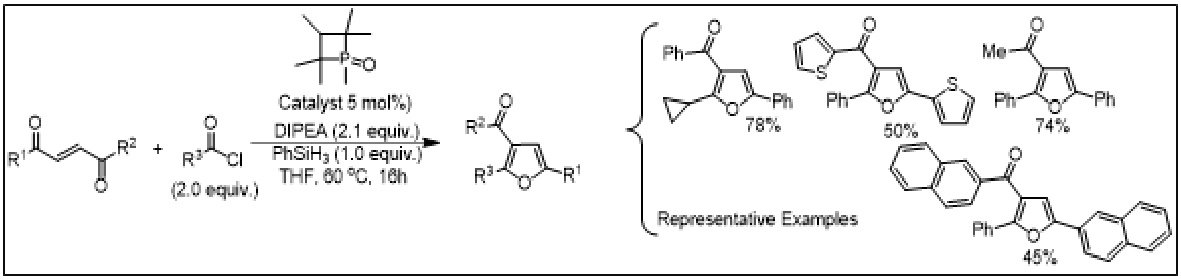
Scheme 11: Synthesis of Substituted Furans via Tandem Acylation–Wittig Reaction

A proposed mechanism for this phospha-Michael addition, followed by *O*-acylation and an intramolecular Wittig reaction, is illustrated in Scheme 12. The process begins with the regioselective nucleophilic addition of Bu$_3$P to *β*-trifluoromethyl *α,β*-enones, forming the zwitterionic intermediate (A). Subsequently, intermediate (A) undergoes acylation with acyl chloride, yielding intermediate (B). This intermediate is then deprotonated by Et$_3$N, generating ylide (C). Finally, an intramolecular Wittig reaction involving ylide (C) results in the formation of trifluoromethylated furan (D).



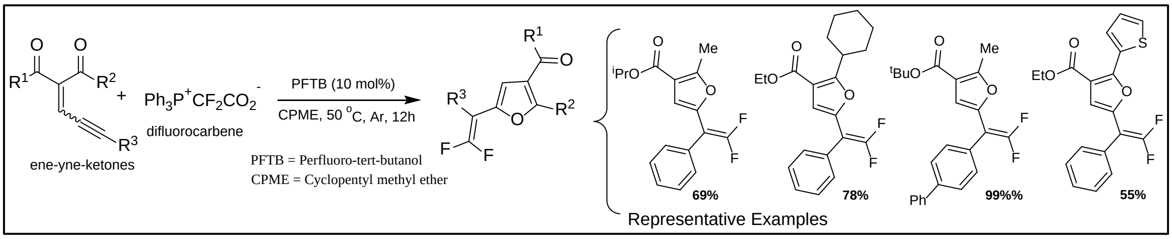
Scheme 12: Plausible Reaction Mechanism

Tönjes, Medvarić and Werner (2024) reported the synthesis of tri-tetrasubstituted furans starting from activated alkenes and acyl chlorides using a phospholene or phosphetane P(III)/P(V) redox cycling catalytic system (Scheme 13). In this transformation, Phenylsilane (PhSiH$_3$) is used as a terminal reductant, which reduces the formed phosphine oxides in the catalytic cycle.



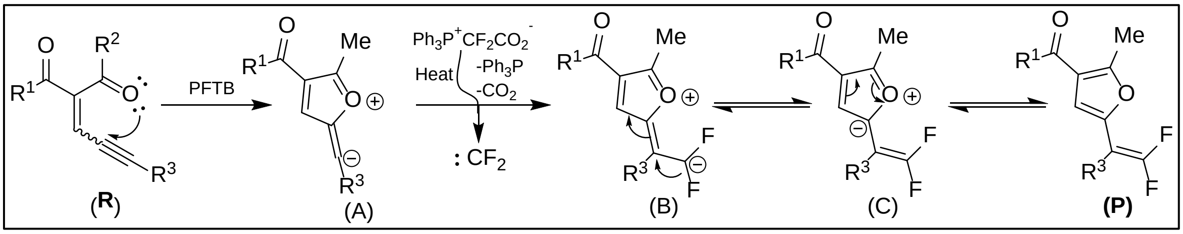
Scheme 13: Synthesis of Tri-substituted Furan by P(III)/ P(V) Redox Cycling Catalysis

Very recently, Li *et al.* (2025) demonstrated a facile synthesis of furan-substituted gem difluoroalkenes using conjugated ene-yne-ketones as the furan source and $Ph_3P^+CF_2CO_2^-$ as an efficient difuoro carbene (:CF_2) source mediated by PFTB-promoted cross-coupling strategy (Scheme-14). It is worth noting that furan-substituted gem-difluoroalkenes serve as bioisosteres of the α-carbonyl furan framework, a key structural motif commonly found in natural products and potential drug candidates.



Scheme 14: Synthesis of Substituted Furan with Gem Difluoroalkenes

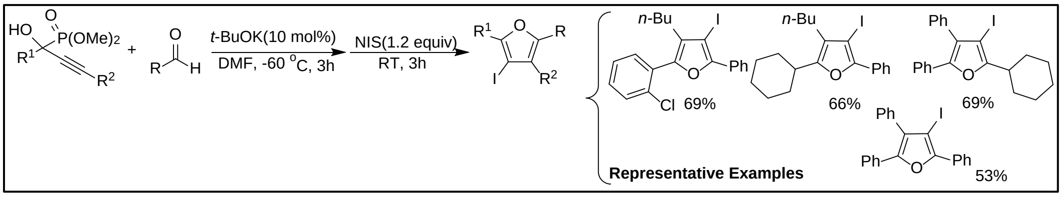
The authors proposed a most probable reaction mechanism based on their controlled experiment results (Scheme 15). The conjugated eneyne ketone (1) is initially activated by $(CF_3)_3COH$ (PFTB). This promotes an intramolecular nucleophilic attack by the carbonyl oxygen, forming a stabilised zwitterionic intermediate A. The vinyl anion in A then rapidly traps a difluorocarbene (:CF_2) which is generated from thermal decomposition of $Ph_3P^+CF_2CO_2^-$, yielding intermediate B/C. Tautomerisation of B/C ultimately gives the desired furan-substituted gem-difluoroalkene -P.



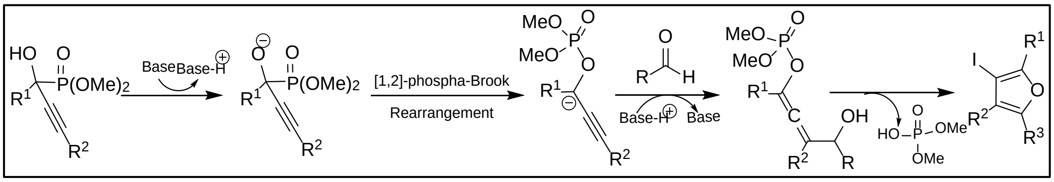
Scheme 15: Proposed Reaction Mechanism for the Formation of Furan-Substituted Gem-Difluoroalkene

Synthesis of Substituted Furan through Cyclo-Addition Reaction

Kondoh and colleagues (2020) developed an efficient approach for synthesising tetrasubstituted furans *via* a [3 + 2] cycloaddition strategy, utilising the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis (Scheme-16). This two-step, one-pot formal cycloaddition involves the nucleophilic attack of an α-oxygenated propargyl anion—generated in situ through the [1,2]-phospha-Brook rearrangement—on an aldehyde at the γ-position, followed by NIS-mediated intramolecular cyclisation (Scheme-17). The process selectively yields 2,4,5-trisubstituted-3-iodofurans bearing diverse substituents. This methodology, employing readily accessible starting materials, offers a valuable route to structurally diverse tetrasubstituted furan.

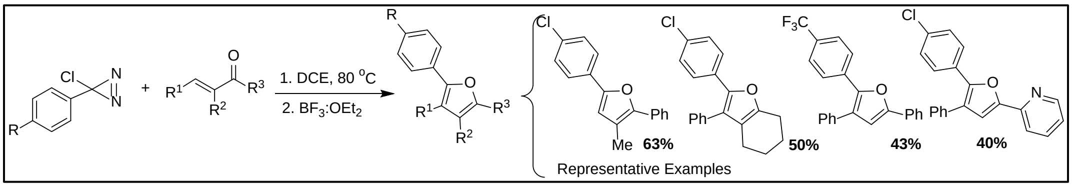


Scheme 16: Synthesis of Tetrasubstituted Furans Utilising [1,2]-Phospha-Brook Rearrangement



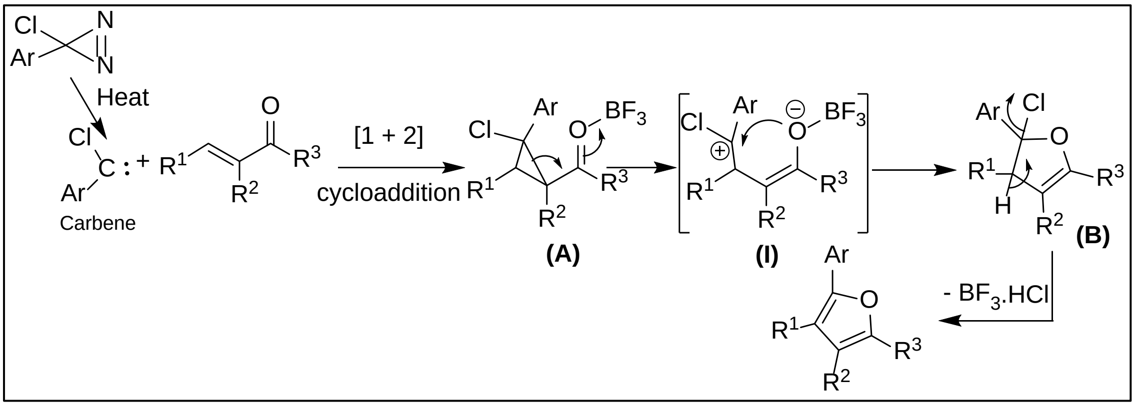
Scheme 17: Proposed Reaction Mechanism

Zhang *et al.* (2022) have recently introduced a convenient one-pot strategy for synthesising di-, tri-, and even tetra-substituted furans in moderate to good yields. This method utilises readily accessible starting materials and employs cost-effective boron trifluoride as a catalyst (Scheme-18). Notably, the process is both metal- and oxidant-free. It involves the cyclopropanation of α,β-alkenyl ketones with phenylchlorocarbene, followed by a BF_3-mediated ring-opening and cyclo-isomerisation *via* a Cloke–Wilson rearrangement, culminating in HCl elimination to form multi-substituted furans. This protocol offers operational simplicity, mild reaction conditions, and broad substrate compatibility, making it an efficient route to synthetically and biologically valuable furan derivatives.



Scheme 18: Synthesis of Substituted Furan through BF_3:Et_2O Mediated Formal [4 + 1] Reaction

To gain insight into the reaction mechanism, the authors conducted a series of control experiments. A simplified representation is provided in Scheme-19. Upon thermolysis, the precursor 3-halo-3-phenyldiazirine undergoes decomposition to generate the electrophilic singlet phenyl-halo-carbene (PhClC:). This reactive carbene rapidly engages in a [1 + 2] cycloaddition with the α,β-alkenyl ketone, yielding a halocyclopropyl ketone intermediate (A). The introduction of $BF_3 \cdot Et_2O$ facilitates the Cloke–Wilson rearrangement of intermediate A, producing a key zwitterionic species (I). Intramolecular cyclisation of intermediate I then furnish dihydrofuran B, which undergoes elimination of HX in the presence of BF_3 to afford the final furan product (Scheme-19).

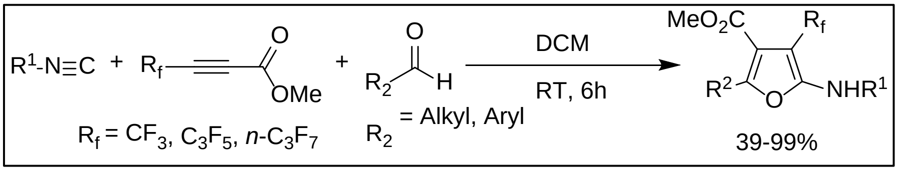


Scheme 19: A Plausible Reaction Mechanism

Synthesis of Substituted Furan through Multicomponent Reaction

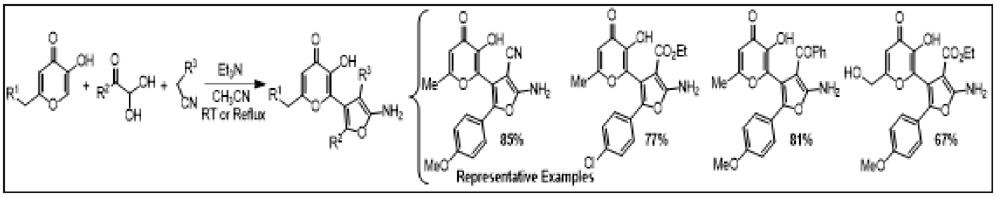
The synthesis of fluorine-containing furan scaffolds presents a significant challenge due to their structural complexity. However, these fluorinated furan derivatives are of great interest because they exhibit valuable pharmacological activities, including anti-HIV, antibacterial, and antiparasitic effects.

In 2019, 2-amino-3-perfluoroalkylfurans were successfully synthesised *via* a multicomponent reaction involving aldehydes, isocyanides, and methyl perfluoroalk-2-ynoates as the starting materials (Wang *et al*., 2019) (Scheme 20).



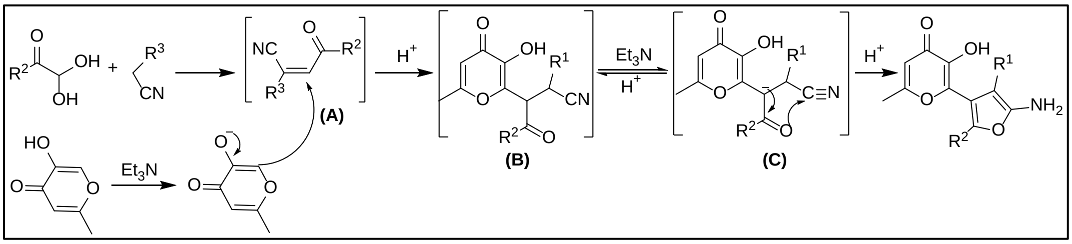
Scheme 20: Synthesis of 2-amino-3-perfluoroalkylfurans through Multicomponent Reaction

Komogortsev and colleagues (2020) developed an efficient one-pot method for synthesising a variety of substituted 2-aminofurans. This strategy involves a multicomponent reaction between 3-hydroxy-4H-pyran-4-ones, α-ketoaldehydes, and methylene-active nitriles (Scheme 21). The approach stands out for its operational simplicity and effectiveness, offering a straightforward route to access the 2-aminofuran framework. Key advantages of the method include high product yields, mild reaction conditions, good atom economy, and a straightforward purification process.



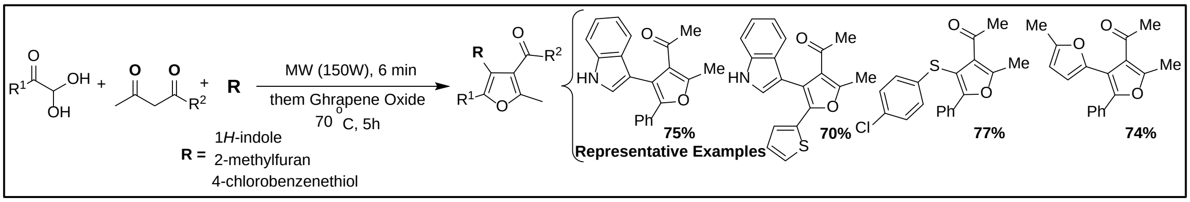
Scheme 21: Synthesis of 2-aminofuran Derivatives via Multicomponent Reaction

A plausible mechanism for this transformation as suggested by the authors has been presented below (Scheme 22)-



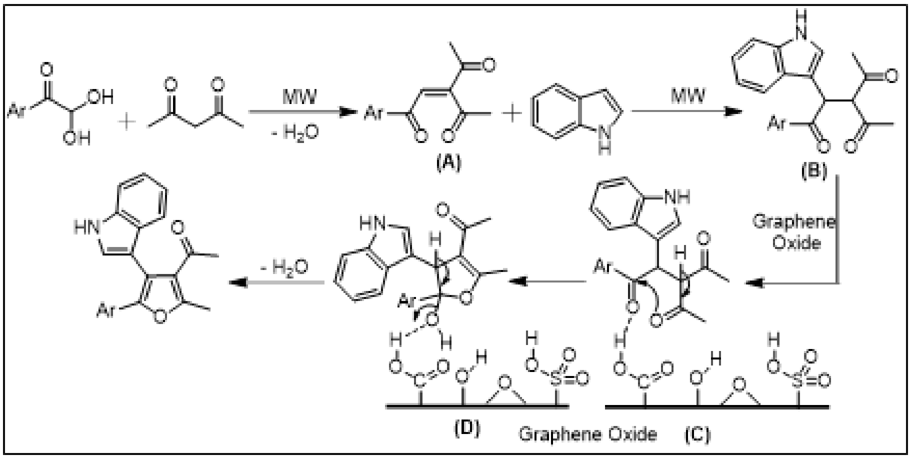
Scheme 22: Proposed Reaction Mechanism for the Formation of 2-aminofurans

In 2020, Jana, Adhikary and Pramanik introduced a highly effective method utilising graphene oxide as a catalyst in a microwave-assisted, one-pot process for synthesising densely substituted furan derivatives. This approach, which started with basic compounds like 1,3-diketones, arylglyoxal and indole or benzothiophenol, etc., demonstrated a broad reaction scope. The team successfully synthesised various multi-substituted indole–furan conjugates, achieving excellent compatibility with a range of functional groups (Scheme 23).



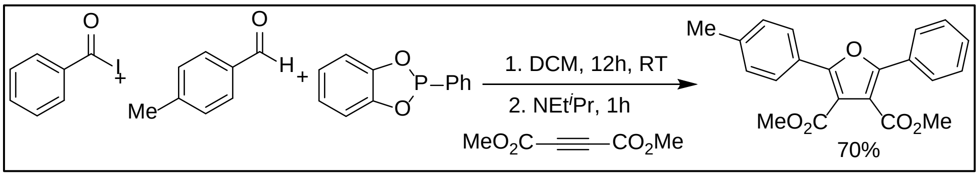
Scheme 23: Graphene Oxide Catalysed MW-assisted One-pot Synthesis of Densely Substituted Furan

The proposed mechanism for the multicomponent reaction is depicted in Scheme 24. Initially, arylglyoxal participates in an aldol-type condensation with a 1,3-diketone, which is subsequently followed by a Michael addition with indole, resulting in the formation of intermediate A. This is followed by a Paal–Knorr cyclisation, facilitated by graphene oxide (GO), leading to the formation of intermediate B and ultimately yielding the desired furan-based product. The oxygen-rich surface of GO—featuring groups like epoxy, hydroxyl, carboxyl, and sulfonic acid—provides both hydrophilic and acidic conditions that are crucial for driving the reaction forward.



Scheme 24: Proposed Reaction Mechanism of Graphene Oxide Catalysed Furan Synthesis

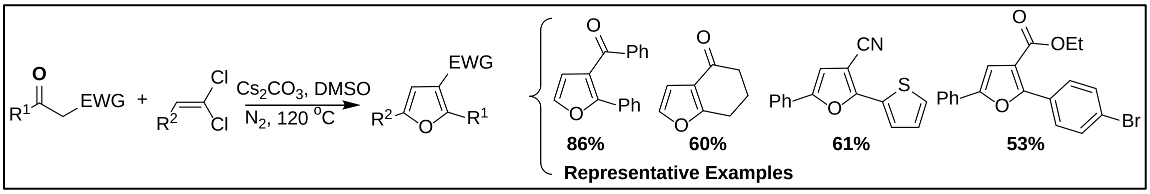
Very recently, Erguven, Zhou and Arndtsen (2021) have described a modular method to construct furans from aldehydes, acyl chlorides and alkynes (Scheme 25).



Scheme 25: Synthesis of Substituted Furan through Multicomponent Reaction

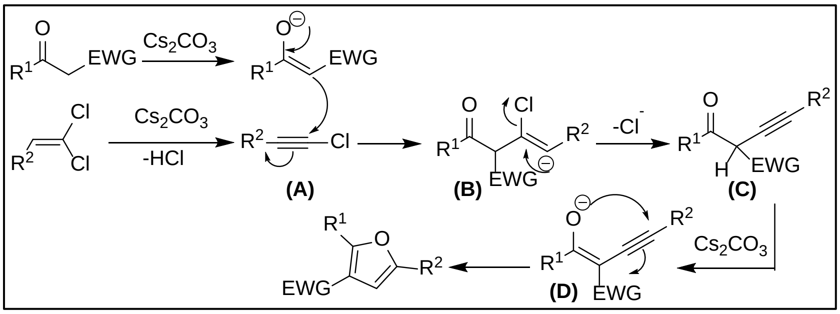
Base Mediated Synthesis of Substituted Furans:

In 2020, You and colleagues introduced an innovative, transition-metal-free approach for synthesising polysubstituted furans using inexpensive and readily accessible starting materials. This base-mediated method effectively accommodates a wide range of β-keto substrates—such as β-diketones, β-ketoesters, β-ketosulfonyls, and β-ketonitriles—along with vinyl dichlorides, enabling the efficient formation of 2,3-disubstituted and 2,3,5-trisubstituted furans with moderate to excellent yields (Scheme-26).



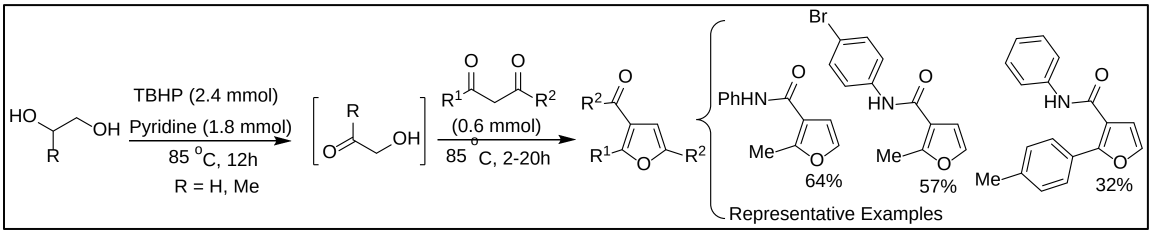
Scheme 26: Transition-metal-free Approach to Polysubstituted Furans

The proposed reaction mechanism is illustrated in Scheme 27. Under basic conditions, the elimination of 1,1-dichloroalkene leads to the formation of the key intermediate, alkynyl chloride (A). This intermediate then undergoes a nucleophilic α-addition by the anionic species generated from deprotonation of the *β*-keto compound, resulting in intermediate (B). A subsequent elimination from (B) gives rise to the *β*-ketoalkyne intermediate (C). Finally, an intramolecular cycloisomerisation of intermediate (C) through the enolate form (D), promoted by the basic environment, yields the desired polysubstituted furan products (Scheme 27).



Scheme 27: Proposed Reaction Mechanism of Base Mediated Furan Synthesis

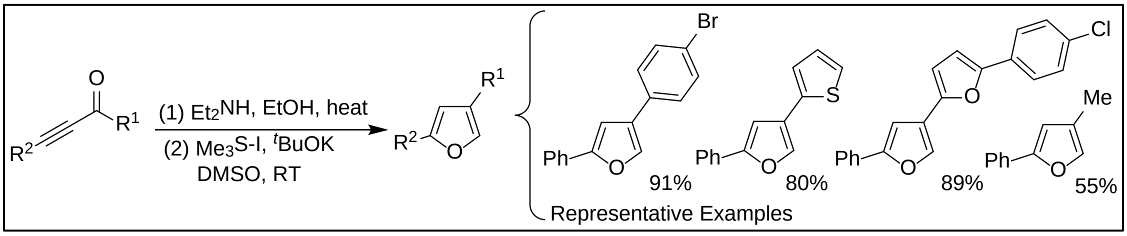
An oxidative synthetic route that excludes the use of transition metals has been developed for producing substituted furans from *β*-ketoanilides and vicinal diols (Maity & Panda, 2025). This methodology is compatible with a diverse array of functional groups, including halogens, methoxy, methyl, and nitro, and allows for the regioselective synthesis of 2,3-disubstituted and 2,3,5-trisubstituted furans through base-induced oxidative C–C and C–O bond formation (Scheme 28). Furthermore, the approach has been extended to the regioselective construction of substituted pyrroles from *β*-ketoenamines, utilising ethylene glycol as a two-carbon source. Key benefits of this strategy include straightforward execution, gentle reaction conditions, broad functional group compatibility, and notably, the elimination of both solvents and hazardous transition metal catalysts.



Scheme 28: Synthesis of Substituted Furan from β-ketoanilides and Vicinal Diols

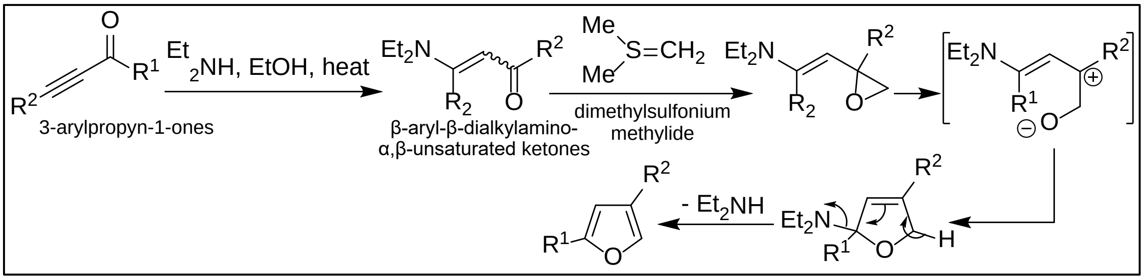
Synthesis of Substituted Furans Using Various Green Methodologies

Very recently in 2023, a method for the synthesis of unsymmetrically substituted furans based on the extended Corey−Chaykovsky reaction has been developed (Shcherbakov *et* *al.,* 2023). The method is characterised by simple reaction conditions and reagents, high yields, and a wide range of formed products (Scheme-29).



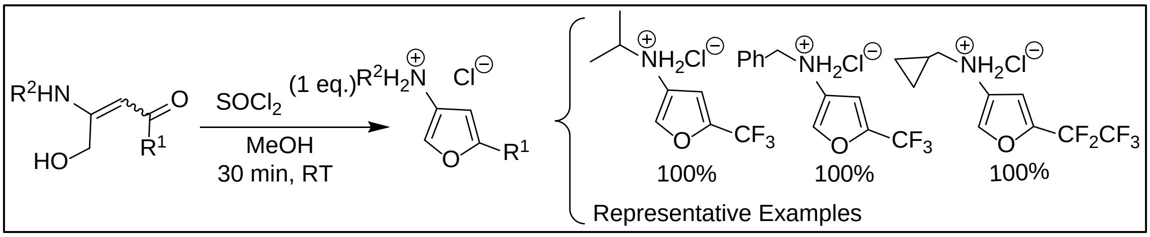
Scheme 29: Synthesis of Substituted Furan via Extended Corey−Chaykovsky Reaction

The initial compounds used are *β*-aryl-*β*-dialkylamino-*α,β*-unsaturated ketones, which can be readily synthesised through the Michael addition of diethylamine to 3-arylpropyn-1-ones (Scheme-30). When these resulting enamines react with dimethylsulfonium methylide, a cascade reaction occurs, resulting in the formation of 2,4-disubstituted furans.



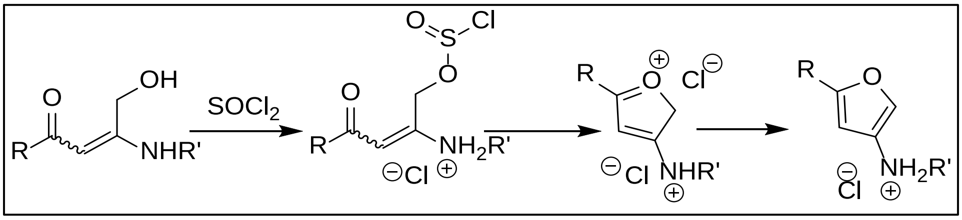
Scheme 30: Proposed Reaction Mechanism

A straightforward methodology has been recently developed for the synthesis of 3-amino-5-fluoroalkylfurans in quantitative or nearly quantitative yields starting from fluoroenones (Plaçais *et al*., 2021) (Scheme-31).



Scheme 31: Synthesis of Substituted Furan via Intramolecular Cyclisation Reaction

In terms of the cyclisation mechanism, the authors propose that the reaction begins with the activation of alcohol by thionyl chloride (see Scheme 32). This is followed by a nucleophilic attack from the oxygen lone pair of the enone onto the α-carbon of the activated alcohol, leading to the formation of a five-membered ring. Subsequent aromatisation then yields the furan product.



Scheme 32: Proposed Reaction Mechanism of Synthesis of 3-Amino-5-fluoroalkylfurans

Conclusion

In summary, this book chapter documents various metal-free approaches developed over the past five years for the synthesis of poly-substituted furans. Several attractive catalytic methodologies – such as those involving iodine, *N*-heterocyclic carbenes (NHCs), and acids – have been reviewed, along with representative examples of substituted furans synthesised *via* these methods.

The corresponding mechanistic pathways for these transformations are also presented. Additional metal-free approaches, including phosphine-mediated synthesis, cycloaddition reactions, and multicomponent reactions, are discussed with relevant examples and mechanisms. Finally, two noteworthy methodologies based on the extended Corey–Chaykovsky reaction and thionyl chloride-mediated synthesis of substituted furans are explored. In conclusion, this chapter offers helpful information regarding the importance and recent advancements in the sustainable synthesis of substituted furan scaffolds, which serve as crucial building blocks in both synthetic and biological chemistry.

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