Syntheses of polysubstituted furans: recent developments

Stefan F. Kirsch*

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Despite attracting tremendous interest for well over a century, the field of furan syntheses is continuously and rapidly developing. This brief overview highlights recent progress in the syntheses of polysubstituted furans primarily guided by substitution pattern. Accordingly, methods are categorized as providing access to either di-, tri- or tetrasubstituted furans.

Introduction

Polysubstituted furans represent an important class of five-membered heterocycles that can be broadly found as structural elements of many natural products and pharmaceutically important substances.[1] Furthermore, they can be employed as useful intermediates in synthetic chemistry.[2] Therefore, a tremendous number of synthetic methods to approach substituted furans is known.[3] The most frequently used methods include the cyclocondensation of 1,4-dicarbonyl compounds (Paal–Knorr synthesis),[4] and the classical Feist–Benary synthesis.[5] Although these methods have proven very useful for the synthesis of furan derivatives, there are some limitations, including the difficulty in accessing furans that contain sensitive functional groups and the inability to provide furans with high flexibility regarding their substitution pattern. For these reasons, the development of even newer and more efficient methods for the synthesis of highly functionalized furans under mild conditions remains an area of ongoing interest.

Most, but not all furan syntheses can be generally divided into two categories: the first, functionalization of existing furan-containing precursors by introduction of new substituents, and the second, construction of the heterocyclic core by cyclization of acyclic substrates.[1] This article provides a personal selection among recent examples of these two categories. The focus lies on methods that allow the mild and selective formation of polysubstituted furans offering a synthetic advantage over previously reported procedures.

Department Chemie, Technische Universität München, Lichtenbergstr. 4, D-85747 Garching, Germany. E-mail: stefan.kirsch@ch.tum.de; Fax: +49 89 2891 3315; Tel: +49 89 2891 3229

Stefan F. Kirsch was born in Berlin, Germany, in 1976. He received his Diploma degree in chemistry from Philipps-Universität Marburg in 2000, and completed his doctoral dissertation in 2003 with Professor Thorsten Bach at the Technical University of Munich. After a postdoctoral fellowship (Alexander von Humboldt) with Professor Larry E. Overman at the University of California, Irvine, he joined the faculty at the Technical University of Munich, where he has started his independent research career. His work focuses on the development of new transition metal mediated reactions for the synthesis of heterocyclic compounds, and their applications in total synthesis.

Stefan F. Kirsch

Functionalization of existing furans

The methods based on functionalization of existing furan precursors are typically not general. For example, derivatization of furans *via* electrophilic substitution is somewhat restricted due to the low stability of furans under acidic and aerobic conditions.[1] Methods involving the metalation of furan derivatives followed by quenching with various electrophiles are mostly limited to base-stable furans.[3d] An interesting metalation protocol that partially overcomes the latter limitation is reported by Knochel and co-workers.[6] Therein, halogen–magnesium exchange becomes an attractive method to generate positionally stable functionalized furylmagnesium compounds under mild conditions tolerating various functional groups such as esters, nitriles or amides. Thus, furan **1** bearing an electron-withdrawing ester underwent an exchange to give the magnesiated species **2**. The subsequent reaction with iminium salt **3** provided 2,5-disubstituted furan **4** containing a propargylic amine functionality (Scheme 1). The magnesiation protocol can also be applied to multiply halogenated furans which undergo a single regioselective halogen–magnesium exchange. Starting from dibrominated furan **5**, this strategy was utilized for the construction of the advanced intermediate **6** in a synthetic approach to furanocembrane carbon skeletons.[7] Since further substitution of the remaining bromine can easily be achieved using a variety of methods, the magnesiation protocol offers a mild access to multiply substituted furans that are otherwise difficult to prepare. Furthermore, it provides a powerful alternative to the well established regioselective cross-coupling

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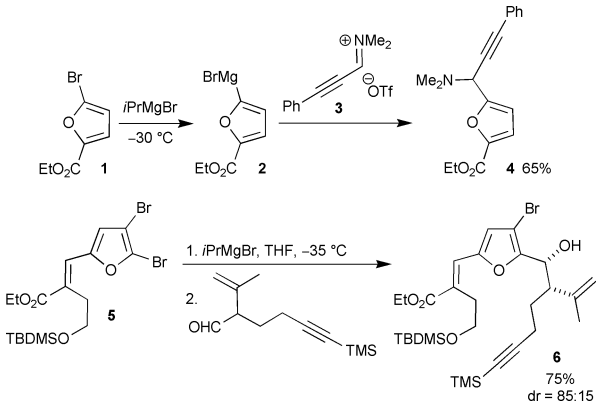
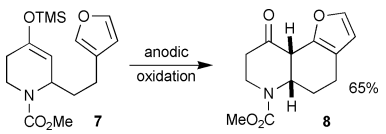


Scheme 1 Functionalized furans by halogen–Mg exchange.

reactions of polyhalogenated furans which failed in the case of furan **5**.[8]

Recent investigations by Wright and co-workers examined an electrooxidative coupling of furans and silyl enol ethers for the assembly of annulated furans.[9] These studies demonstrated that the electrooxidative annulation can be carried out on substrates bearing functional groups, such as olefins, acetals, esters, and carbamates (*e.g.* **7** → **8**; Scheme 2).



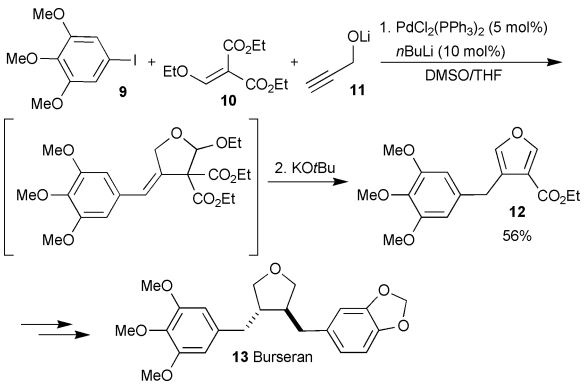
Scheme 2 Electrooxidative synthesis of annulated furans.

Synthesis of furans *via* cyclization reactions

The vast majority of the routes to multiply substituted furans have involved cyclization approaches starting from acyclic precursors. A particularly effective approach is through transition metal catalyzed cycloisomerization of unsaturated acyclic precursors, which usually proceeds under rather mild conditions. Many different strategies involve allenyl ketones as starting materials for furan synthesis mostly using Rh(I), Ag(I), Au(III), and Pd(0/II) compounds as catalysts for 5-*endo-trig* cyclizations.[10] An alternative strategy involves catalyzed cyclization of alkynyl ketones,[10e,11] alcohols,[12] or epoxides.[13] Alkynes are typically considered to be more attractive starting materials than allenes, since practical routes to allenes that contain sensitive functional groups are somewhat limited. Furthermore, transition metal catalyzed cyclization of alkynyl or allenyl substrates has been typically used to prepare di- and trisubstituted furans, while tetrasubstituted furans are not readily accessed. As a consequence, recent research mainly focuses on two developments: expanding the scope of suitable starting materials for these transformations, and minimizing the restrictions in substitution pattern.

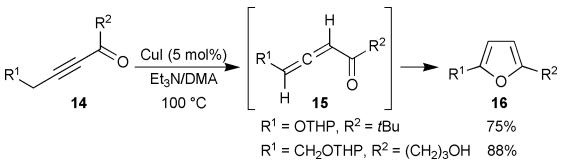
Disubstituted furans

An interesting multicomponent strategy, which involves a conjugate addition, a palladium-catalyzed coupling–cyclization, a decarboxylative elimination and a double bond isomerization, was developed by Balme and co-workers for the synthesis of 3,4-disubstituted furans (*e.g.* **12**) bearing a benzyl group (Scheme 3).[14] Using easily accessible starting materials (**9**, **10**, **11**), the one-pot procedure proved practical for the formal synthesis of (±)-burseran (**13**). An alternative one-pot protocol by Müller and co-workers combines a Sonogashira coupling, an addition of NaI, a cyclocondensation and a subsequent Suzuki coupling to prepare 2,4-disubstituted furans in reasonable yields.[15]



Scheme 3 One-pot synthesis of 3,4-disubstituted furans.

Gevorgyan and co-workers[16] have investigated the utility of alkynyl ketones **14** as readily available starting materials for the synthesis of 2,5-disubstituted furans. The Cu(I)-catalyzed and base-assisted cycloisomerization is believed to proceed through the intermediary allenyl isomer **15** (Scheme 4). The method gave furans **16** possessing different functional groups, such as alkenes, ethers, acetals, esters, and free hydroxyl groups.

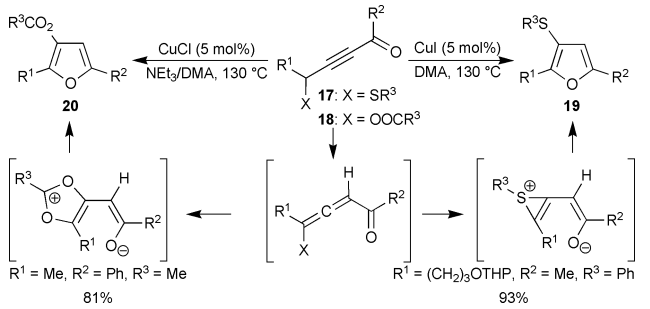


Scheme 4 Cu(I)-catalyzed synthesis of 2,5-disubstituted furans.

Trisubstituted furans

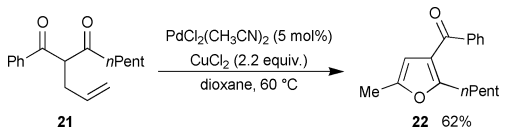
Extension of the methodology developed for preparing 2,5-disubstituted furans was accomplished by using 4-thio- and 4-acyloxybut-2-ynones **17** and **18** in a novel Cu(I)-catalyzed route to trisubstituted furans **19** and **20**, respectively.[17] A key step in the proposed reaction pathway involves a 1,2-migration of the heteroatom-containing groups providing 3-thio-[17a] and 3-acyloxy-substituted[17b] furans (Scheme 5). In the case of 3-acyloxy-substituted furans, the method is reported to be limited to the use of phenyl- and *tert*-butyl alkynyl ketones to obtain the furan products as a single regioisomer. Nevertheless, the synthesis of 3-thio-substituted furans **19** was realized in excellent yields and regioselectivities using a broad variety of substituents for R^2.

Since olefins are more readily accessible than are alkynes and allenes, Widenhoefer and co-worker have studied the utilization of alkenyl substrates as suitable starting materials for the transition metal catalyzed synthesis of furans *via* heterocyclization.[18] For example, α-alkenyl-β-diketone **21** underwent furan formation in



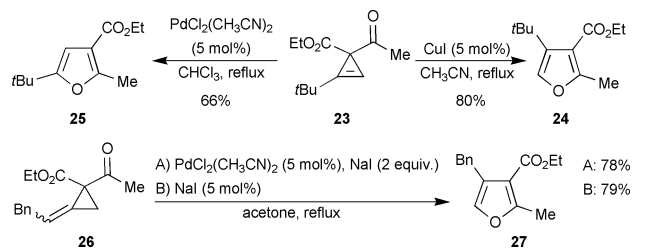
Scheme 5 Synthesis of 3-thio- and 3-acyloxy-substituted furans.

the presence of a Pd(II) source and $CuCl_2$ as an oxidant to provide the trisubstituted furan **22** in 62% yield (Scheme 6). However, variation of the substituents remains limited using this protocol.



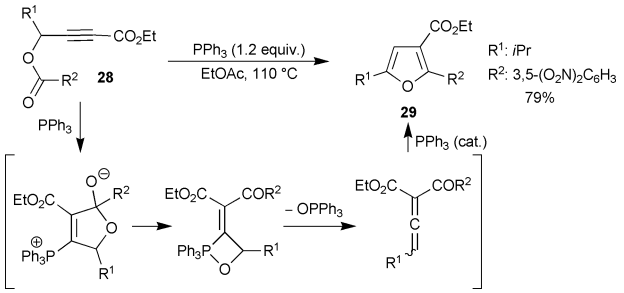
Scheme 6 Oxidative alkoxylation of an α-alkenyl-β-diketone.

A fascinating strategy for the synthesis of trisubstituted furans, which begins with cyclopropenyl ketones **23** or alkylidenecyclopropyl ketones **26**, was developed by Ma and co-workers (Scheme 7).[19] Cycloisomerization of cyclopropenyl ketone **23** provided the 2,3,4-trisubstituted furan **24** with excellent regioselectivity using CuI as the catalyst; the 2,3,5-trisubstituted furan **25** was formed using $PdCl_2(CH_3CN)_2$.[19a] Although the starting cyclopropenes are not so readily accessible, the approach is potentially powerful due to the total control of regioselectivity. Further studies focused on the use of alkylidenecyclopropyl ketones **26** as starting materials in a ring-opening cycloisomerization sequence.[19b] The generality of this approach was explored using catalytic amounts of $PdCl_2(CH_3CN)_2$ and NaI to provide the trisubstituted furans **27**. In the absence of NaI, the formation of 4*H*-pyrans was observed. Moreover, treatment of alkylidenecyclopropyl ketones with 5 mol% of NaI led to the formation of the corresponding furans, although not as cleanly and rapidly as in the presence of a Pd(II)-catalyst. A speculative rationale to account for this effect has been proposed.



Scheme 7 Ring-opening cycloisomerization approach to furans.

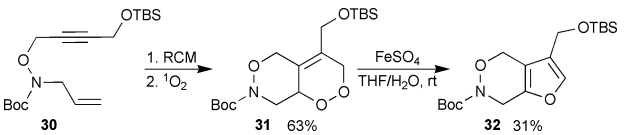
Another mechanistically novel protocol provides access to di- and 2,3,5-trisubstituted furans **29** *via* a phosphine mediated reductive cyclization reaction of γ-acyloxy butynoates **28** (Scheme 8).[20] It is suggested that the reaction proceeds *via* a betaine intermediate, which after the loss of phosphine oxide gives allenic ketones as furan precursors. Perhaps most importantly, γ-acyloxy butynoates



Scheme 8 Phosphine-mediated synthesis of trisubstituted furans.

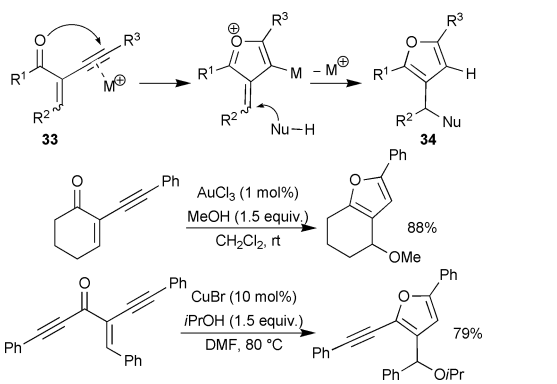
are readily obtained through the condensation of ethyl propiolate with aldehydes followed by acylation.

An alternative reaction sequence, which begins with a ring-closing metathesis of acyclic enynes **30** followed by a Diels–Alder reaction with singlet oxygen, was developed by Tae and co-workers to give the trisubstituted furans **32** (Scheme 9).[21] The intermediary 1,2-dioxines **31** were converted into the furans by treatment with $FeSO_4$ in varying yields. Subsequent reductive cleavage of the N–O bond enhances the utility of this method.



Scheme 9 RCM–Diels–Alder sequence.

2-(1-Alkynyl)-2-alken-1-ones **33** have been employed in numerous ways as suitable starting materials for the construction of furans **34**.[22] It is proposed that a transition metal catalyzed cyclization forms an oxonium ion intermediate that is trapped by various nucleophiles (Scheme 10). For example, Larock and co-workers have described the reaction catalyzed by $AuCl_3$ to give trisubstituted furans with high diversity.[22a,b] A survey of other transition metal salts demonstrated that the optimum catalyst in CH_2Cl_2 at room temperature is $AuCl_3$ based on reaction time and yield. Yamamoto and co-workers have also reported cyclization of 2-(1-alkynyl)-2-alken-1-ones, in this case catalyzed by CuBr.[22c] In these studies, the selection of the solvent proved to be critical. Whereas cyclization in DMF at 80 °C delivered the corresponding furans in good yields, use of other solvents did not give furan formation.



Scheme 10 Synthesis of furans from 2-(1-alkynyl)-2-alken-1-ones.

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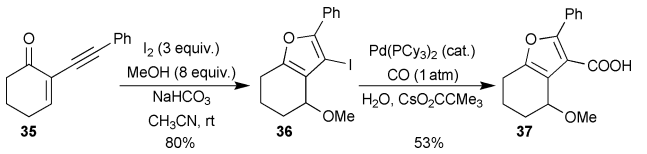
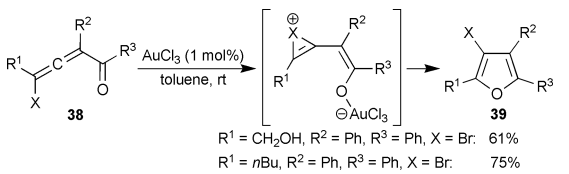
Tetrasubstituted furans

As an extension of their investigations of the utility of 2-(1-alkynyl)-2-alken-1-ones for forming furans, Larock and co-workers studied cyclizations induced by an electrophile.[22b] The products of transformations of this type[22d] are iodine-containing tetrasubstituted furans which are useful intermediates for the synthesis of more complex products using known palladium chemistry. Furyl iodide **36**, which was derived from iodine induced cyclization of 2-(1-alkynyl)-2-alken-1-one **35**, was further functionalized to provide furanoic acid **37** (Scheme 11).



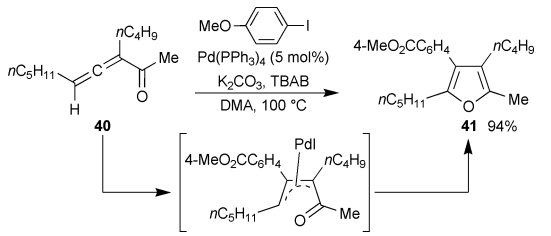
Scheme 11 Electrophilic cyclization of 2-(1-alkynyl)-2-alken-1-ones.

A Au(III) catalyzed selective cycloisomerization of haloallenyl ketones **38** was used by Gevorgyan and co-workers[23] to construct di-, tri-, and tetrasubstituted furans **39** with a halogen at the 3-position (Scheme 12). A mechanism *via* a halirenium intermediate and involving a 1,2-migration of the halogen is proposed. It is notable that the use of gold(III) was required to obtain the 3-halofurans with high selectivity. In the presence of $(Et_3P)AuCl$, the 2-halofurans were formed exclusively. The reaction may be compatible with a wide variety of functionalities. A Ag(I) catalyzed sequence proceeding *via* similar intermediates gave tetrasubstituted furans, which contain sulfonyloxy, phosphatyloxy or acyloxy groups at the 3-position.[17b]

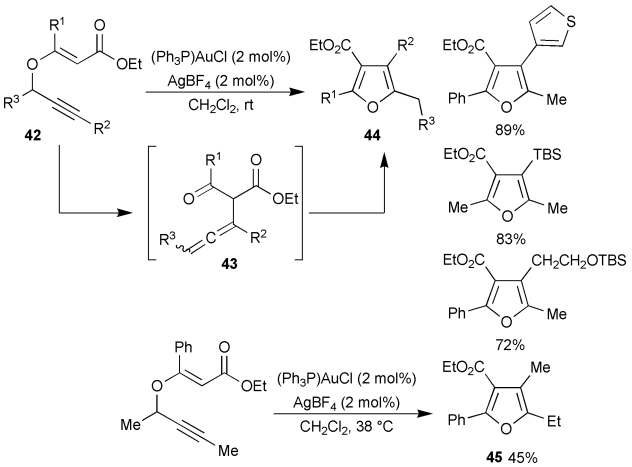


Scheme 12 Synthesis of halofurans from haloallenyl ketones.

Starting from allenyl ketones,[10] the introduction of substituents at the 4-position of the corresponding furans using a transition metal catalyzed cycloisomerization approach is difficult. Recent investigations by Ma and co-workers examined a Pd(0)-catalyzed cross-coupling cyclization sequence to form tetrasubstituted furans **41** from 1,2-allenyl ketones **40** (Scheme 13).[24] On the basis of the proposed mechanism, it appears that the scope of the process may easily be extended to substituents other than simple aryls and alkyls which have been used so far.



Scheme 13 Coupling cyclization approach to tetrasubstituted furans.



Scheme 14 Synthesis of tetrasubstituted furans *via* a propargyl-Claisen rearrangement–cyclization cascade.

A cascade reaction of a propargyl-Claisen rearrangement and heterocyclization was employed by Kirsch and co-workers in efforts towards the synthesis of tetrasubstituted furans (Scheme 14).[25] The strategy underlying this synthetic approach was to catalyze a formal [3,3]-sigmatropic rearrangement of propargyl vinyl ethers **42**. A transition metal catalyzed cyclization of 2,3-allenyl ketone intermediates **43** would then generate the fully substituted furans **44**. A variety of acceptor substituted propargyl vinyl ethers were surveyed for this transformation using cationic triphenylphosphinegold(I) complexes as efficient catalysts for both steps in the reaction cascade. It is important to note that gold(III) complexes failed to give the desired furans in high yields. The acceptor substituents in the 3-position do not necessarily have to be esters. Gratifyingly, the reaction also takes place with ketones and amides.[26] Utilizing this protocol, trisubstituted furans are also accessible ($R^1 = H$ or $R^2 = H$). The transformation **42** → **44** demonstrates the remarkable functional group tolerance of gold(I)-catalyzed reactions. Moreover, it is not necessary to take special precautions to exclude air and moisture from the reaction mixture. Preliminary experiments indicated that heterocyclization forming furans with substituents other than methyl at the 5-position ($R^3 \neq H$) was slow under the influence of the standard catalyst system. For example, 5-ethylfuran **45** was obtained in 45% yield after 24 h at 38 °C. Other transition metal catalysts might be effective in overcoming this limitation. The strategy employed in this synthesis differs from almost all other applications of transition metal catalyzed cyclization reactions of allenyl ketones, as allenyl ketones are typically used in a 5-*endo* cyclization making it difficult to introduce substituents at the 3- and/or 4-positions. The 5-*exo*-*dig* cyclization of 2,3-allenyl ketone precursors **43** represents a significant departure from this conventional strategy. Of primary importance, propargyl vinyl ethers **42** are easily accessible from propargyl alcohols and 2-propynoic acid derivatives.

Conclusions

The creative assemblies of furans highlighted herein demonstrate that a manifold of powerful methods is available to access polysubstituted furans. Due to functional-group tolerance, the

use of readily accessible precursors, and predictable selectivity for the introduction of substituents, these methods facilitate the synthesis of various furans with regard to their substitution pattern. However, it is important to point out that every method has some limitations. In view of the ongoing importance of heterocyclic compounds in various fields, the development of even more general methods for furan synthesis will certainly play a key role in the diversity-oriented synthesis of this important class of compounds.[27]

It is certain that many more protocols for the construction of polysubstituted furans will be described in the future. Two future trends are easy to predict: a larger variety of methods will be available for economic and environmetally friendly furan syntheses on larger scales, and a larger variety of processes combining ease of access to starting materials and flexibility of the substitution pattern will be developed.

Acknowledgements

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