Synthesis of Cyclopropyl-Substituted Furans by Brønsted Acid Promoted Cascade Reactions

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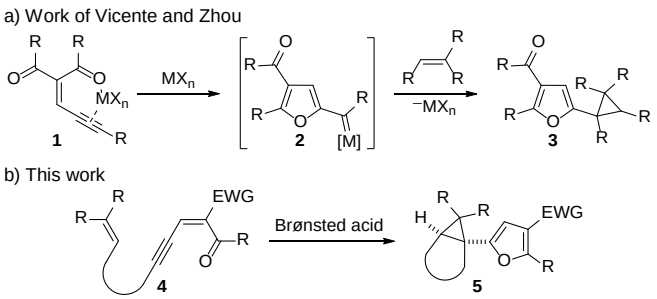
Abstract: *Chloroacetic acid promotes an efficient and diastereoselective intramolecular cascade reaction of electron-deficient ynenones to deliver products featuring a 2,3,5-trisubstituted furan bearing a fused cyclopropyl substituent at the 5-position. Synthetically relevant polycyclic building blocks featuring various size rings and heteroatoms have been synthesized in high yield using this mild acid-catalysed reaction.*

Furans occur frequently as sub-units of natural products,[1] bioactive compounds[2] and functional materials,[3] and they are also valuable synthetic building blocks that can be transformed into many other functional groups.[4] The importance of furans has led to the development of a wide range of methods for their synthesis.[5] In addition to traditional methods,[6] metal-mediated synthesis of furans using copper,[7] zinc,[8] palladium[9] and gold[10] catalysts has become popular. A few organocatalytic processes for the synthesis of furans have also been described,[11] including the tetrahydrothiophene-catalysed synthesis of highly substituted furfuryl alcohols and amines developed by our group recently.[12]

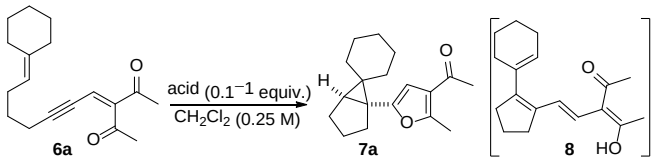
Cyclopropanes, despite their ring strain, are found in many natural products including terpenes, pheromones, pyrethroid insecticides, fatty acid metabolites and unusual amino acids.[13] The cyclopropane group is also prevalent in pharmaceuticals and features in members of fluoroquinolone family of antibiotics, the antidepressant tranylcypromine,[14] antipsychotic substances[15] and anti-HIV agents.[16] In medicinal chemistry, a cyclopropane is often used as a bioisostere of an alkene because of its superior metabolic stability.[17] The significant strain present in cyclopropanes makes them challenging to synthesize and they are usually prepared from highly reactive species such as carbenoids, free carbenes,[18] or ylides.[19]

Vicente[8b] and Zhu[10a] recently reported two methods for the synthesis of cyclopropyl furans **3** in which the metal carbenoid **2** is produced directly from an ynenedione **1** (Scheme 1a). On the basis of these reports and results of earlier studies concerning the acid-promoted synthesis of furans from ynenones,[20] we postulated that treatment of the electron-deficient enyne **4** with a Brønsted acid would trigger an intramolecular cascade reaction to produce a highly functionalised cyclopropylfuran (Scheme 1b).



Scheme 1. Cyclopropyl-substituted furan synthesis from carbonyl-conjugated enynes.

Table 1. Summary of optimisation studies.



Entry	Acid	Loading [equiv.]	Solvent	Temp.	Time [h][a]
1	$PhCO_2H$	1.0	CH_2Cl_2	reflux	72
2	$MeCO_2H$	1.0	CH_2Cl_2	reflux	72
3	$ClCH_2CO_2H$	1.0	CH_2Cl_2	reflux	20
4	$(CF_3)_2CHOH$	1.0	CH_2Cl_2	reflux	120
5	CF_3CO_2H	1.0	CH_2Cl_2	reflux	–[b]
6	$ClCH_2CO_2H$	1.0	THF	40 °C	–[c]
7	$ClCH_2CO_2H$	1.0	PhMe	40 °C	20
8	$ClCH_2CO_2H$	0.5	CH_2Cl_2	reflux	24
9	$ClCH_2CO_2H$	0.25	CH_2Cl_2	reflux	24
10	$ClCH_2CO_2H$	0.1	CH_2Cl_2	reflux	–[d]
11	–	–	CH_2Cl_2	reflux	–[e]

[a] Time taken to reach 100% conversion as determined by ^{1}H NMR analysis. [b] The substrate **6a** was consumed after 20 h but only product **8** observed. [c] The substrate **6a** decomposed. [d] Conversion of 33% was observed when the reaction was stopped after 48 h. [e] No reaction observed after 72 h.

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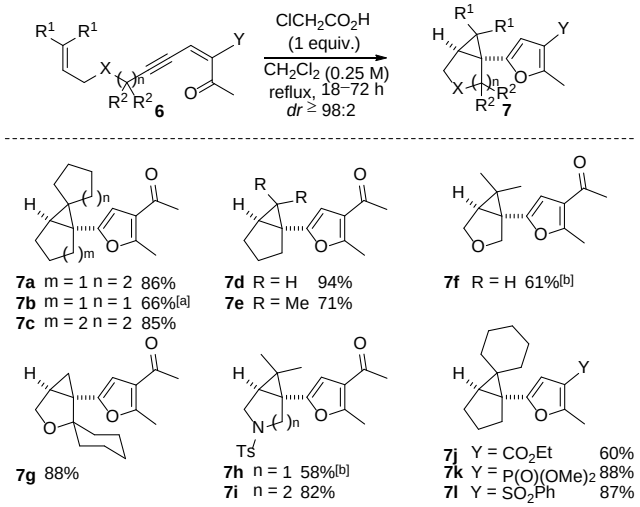
The initial experiment in our study involved reaction of the ynenedione **6a** with a stoichiometric amount of benzoic acid in CH_2Cl_2 at reflux (Table 1, entry 1). Under these conditions, starting material was converted into the furan-containing tetracyclic ketone **7a** (single diastereoisomer)[21] in 72 hours. Several carboxylic acids were screened and it was found that chloroacetic acid (pK_a = 2.9) is optimal (entry 3) and weaker acids, such as acetic (pK_a = 4.8) or benzoic acid (pK_a = 4.2), deliver reduced reaction rates (entries 1 and 2). 1,1,1,3,3,3-Hexafluoro-2-propanol (pK_a = ~11) is also sufficiently acidic to promote the transformation, but it took five days for complete reaction of ynenedione **6a** (entry 4). The use of trifluoroacetic acid (pK_a = 0.2) resulted in the formation of the highly unsaturated by-product **8** instead of the product **7a** (entry 5).

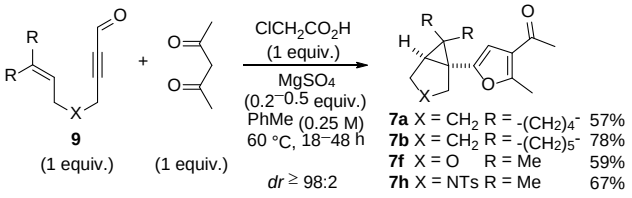


Scheme 2 Scope of the reaction. [a] Yield calculated over two steps because of cyclisation of the substrate **6b** on silica gel. [b] Yield calculated over three steps because of the spontaneous cyclisation of substrates **6f** and **6h**.

The reaction can be performed in CH_2Cl_2 or toluene (entries 3 and 7, Table 1). Furthermore, a sub-stoichiometric amount of acid can be employed to promote the transformation without a significant decrease in reaction rate (entries 8 and 9). However, the reaction rate drops substantially when the amount of acid is reduced to 0.1 equivalents (entry 10). Finally, the crucial role played by the acid is clear because there is no reaction in its absence (entry 11).

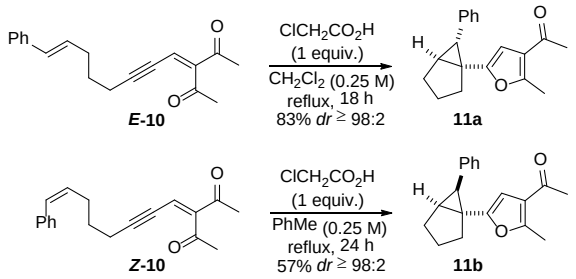
Optimisation experiments showed that the reaction is robust and so the scope was expanded to the preparation of a range of furans bearing a cyclopropyl substituent at the 5-position (Scheme 2). Various substituents on the pendent alkene tethered to the electron-deficient enyne substrate were tolerated. For example, cyclopentylidene and cyclohexylidene substrates underwent cyclisation to give the novel spirocyclic products **7a–c** and **7j–l**. The tether length between the alkene functionality and the electron-deficient enyne was varied to deliver cyclopropanes fused to 5- or 6-membered rings. The formation of polycyclic products incorporating oxygen or nitrogen was also shown to be possible and the synthetically relevant 3-oxa- and 3-aza-bicyclo[n.1.0]alkane derivatives **7f–i** were obtained in good yields. These product are particularly valuable because the bicyclo[n.1.0]alkane motif is present in several natural products and other bioactive compounds.[22] The reaction was also performed on substrates in which one of the carbonyl groups of the diketone was replaced with an alternative electron-withdrawing substituent. When the ketone was replaced with an ester, a phosphonate or a sulfone group, the reaction afforded the corresponding cyclopropyl furans **7j–l** with good to excellent yields. The structures of the novel polycyclic products **7a** and **7c** were confirmed by single crystal X-ray analysis.[21] The ynenediones **6f** and **6h** underwent spontaneous partial cyclisation to deliver the desired cyclopropyl furans **7f** and **7h** immediately after Knoevenagel condensation. Furthermore, the ynenedione **6b** underwent partial cyclisation to give the desired furan **7b** during purification, even though formation of the cyclopropyl furan **7b** was not observed immediately following Knoevenagel condensation.

The substrates **6** were accessed by Knoevenagel condensation reactions of a 2-alkynal **9**. As a consequence of the instability of some substrates and the ability of Brønsted acids to catalyse the Knoevenagel condensation reaction, we investigated the viability of performing condensation and cyclisation in one pot. Pleasingly, when a mixture of the 2-alkynal **9**, acetylacetone, chloroacetic acid and $MgSO_4$ in toluene was heated at 60 °C for 18 hours, the cyclopropyl furans **7a**, **7b**, **7f** and **7h** were obtained in good yield (Scheme 3).



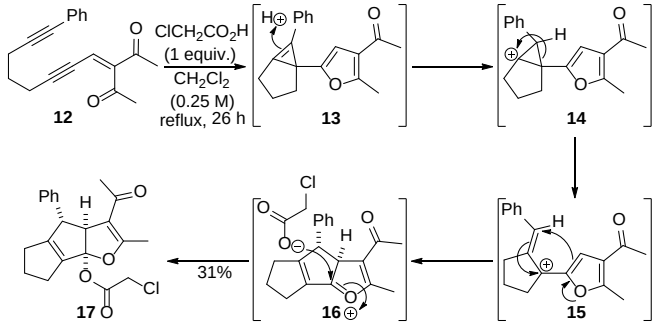
Scheme 3. One-pot synthesis of cyclopropyl furans **7a**, **7b**, **7f** and **7h**.

The influence of the alkene geometry on the outcome of the reaction was explored using substrates ***E*-10** and ***Z*-10** (Scheme 4). When a mixture of the substrate ***E*-10** and chloroacetic acid was heated at reflux in CH_2Cl_2 for 18 hours, the cyclopropane **11a** was obtained in 83% yield as a single diastereoisomer. The reaction of the isomeric compound ***Z*-10** under the same conditions was much slower; incomplete conversion (76%) into furan **11b** was observed after 7 days.[23] However, when a mixture of the ynenedione ***Z*-10** and chloroacetic acid was heated in toluene at reflux for 24 hours there was complete consumption of starting material and the product **11b** was obtained in 57% yield as a single diastereoisomer.[24] The configuration of the alkene has a dramatic influence on the rate of the reaction and, more importantly, is translated directly into the stereochemistry of product. Thus, either diastereomer of the tricyclic compound **11** can be obtained simply by choosing the substrate with appropriate alkene configuration.



Scheme 4. Influence of the alkene geometry on the stereochemical outcome of the cascade reaction.

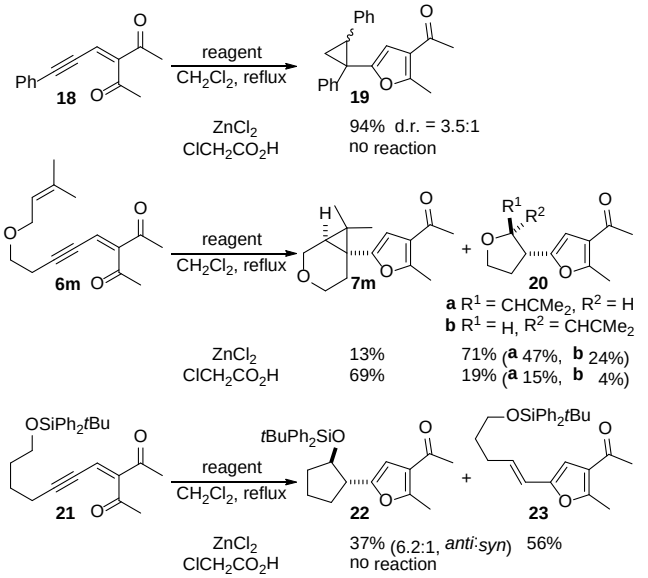
Expansion of the reaction scope to include substrates bearing a pendant alkyne was also investigated. Treatment of the substrate **12** with a stoichiometric amount of chloroacetic acid in CH_2Cl_2 at reflux for 26 hours afforded the tricyclic acetal **17** in 31% yield, the structure of which was confirmed by single crystal X-ray analysis.[21] The reaction is believed to proceed by generation of the cyclopropene **13** followed by protonation to give the cation **14** and then ring opening to give the stabilised cation **15**. Subsequent thermal conrotatory Nazarov-type ring closure of **15** affords oxocarbenium ion **16**, which is trapped by the carboxylate to give the tricyclic acetal **17**.



Scheme 5. Synthesis of tricyclic acetal **17**.

Our results pose interesting questions with regard to the reaction mechanism. One potential mechanism would involve nucleophilic attack of the pendent alkene onto an activated form of the ynenone to generate a cationic centre followed by closure of the three-membered ring. However, results of the reactions presented in Scheme 4 show that cyclopropane C–C bond formation can not occur in a stepwise fashion through an intermediate benzylic carbocation because alkene configuration is translated into product stereochemistry. The fact that the highest yields are obtained for the reactions of **6d** and **6g** to give the furans **7d** and **7g** also rules out a cationic intermediate because it would be primary and therefore very unstable.

An intriguing possibility is the involvement of a free carbene during the acid-catalyzed process. In order to clarify matters, a series of experiments was performed in which the Brønsted acid and Lewis acid catalysed reactions were compared (Scheme 6). In the first set of experiments, the Lewis acid catalysed reaction was performed with intermolecular trapping of the intermediate carbenoid with styrene, as reported by Vicente and co-workers:[8] and results compared to those of the corresponding acid-catalysed process. Exposure of the substrate **18** to zinc(II) chloride in the presence of styrene afforded the cyclopropane **19** as expected. In contrast, the acid-catalyzed reaction failed to deliver the cyclopropane **19** and starting material was recovered.



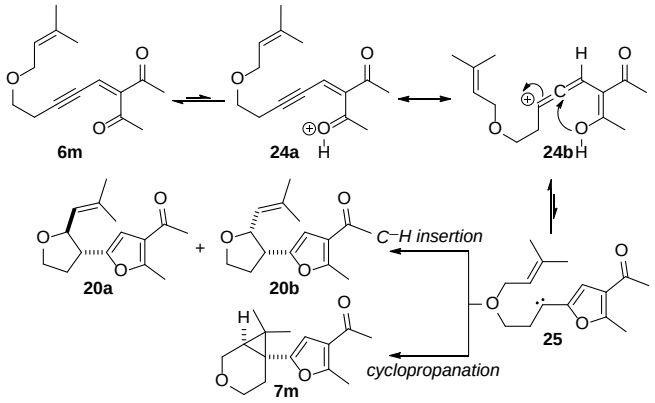
Scheme 6. Comparison of reactions mediated by zinc(II) chloride and those catalysed by chloroacetic acid.

In the second set of experiments, the substrate **6m** was treated with zinc(II) chloride to give a mixture of the expected cyclopropane **7m** along with the diastereomeric tetrahydrofurans **20a** and **20b** resulting from an unprecedented intramolecular C–H insertion reaction of the putative zinc carbenoid (Scheme 6). The corresponding acid-mediated reaction delivered all three products, but the cyclopropane **7m** was now the major product.

In the final set of experiments, the reactions of the substrate **21** were investigated (Scheme 6). The zinc-catalysed reaction afforded a diastereomeric mixture (6.2:1, *anti*:*syn*) of the cyclopentane **22**, arising from intramolecular C–H insertion of the putative zinc carbenoid at the position adjacent to the silyl ether, along with the *E* alkene **23** produced by elimination of the presumed carbenoid intermediate. In contrast, the acid-catalysed reaction afforded neither of these products and starting material was recovered.

Results from the experiments shown in Scheme 4 and Scheme 6 suggest that the acid-catalysed reaction proceeds via a free carbene that can undergo competitive intramolecular cyclopropanation and C–H insertion with allylic ethers such as **6m**, but does not participate in intermolecular cyclopropanation reactions or intramolecular C–H insertion reactions with less reactive substrates. The proposed reaction mechanism accounting for the formation of **7m** and **20a/b** is shown in Scheme 7. Protonation of one of the carbonyl groups of **6m** results in the formation of **24a** which, when considered as resonance form **24b**, can undergo cyclisation by intramolecular nucleophilic attack of the allenic carbon by the enol to give the carbene **25**. The carbene **25** then reacts with the alkene or undergoes allylic C–H insertion to give the products **7m** and **20a/b**. The fact that intermolecular cyclopropanation and intramolecular C–H insertion reactions of less activated substrates are disfavoured suggests that cyclisation to give the furan and carbene is reversible in the absence of a reactive

group that can trap the carbene and that a low concentration of the carbene intermediate is generated from the protonated substrate.



Scheme 7. Proposed mechanism for the acid-catalyzed reaction of **6m**.

In summary, a high-yielding and highly stereoselective Brønsted acid catalysed synthesis of trisubstituted furans bearing a ring-fused cyclopropyl substituent has been developed in which three bonds are created in a single step. Data suggest that the reaction proceeds by an unusual mechanism in which a free carbene is generated under acidic conditions. Studies are underway to expand this method, confirm the reaction mechanism, and apply it to the synthesis of bioactive targets.

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Keywords: furans • cyclopropanes • cascade reactions • enynes • polycyclic compounds

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[21] Structures of compounds **7a** (CCDC 1043529), **7c** (CCDC 1043528) and **17** (CCDC 1043527) were confirmed by X-ray crystallography. Data have been lodged with the Cambridge Crystallographic Data Centre (CCDC). Details can be found in Supporting Information and data can be obtained free of charge from CCDC (www.ccdc.cam.ac.uk).

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[23] See supporting information for further details.

[24] The relative stereochemistry of products **11a** and **11b** was assigned by comparison of the coupling constants between the cyclopropyl protons in the ^{1}H NMR spectrum of each compound. Values of J = 4.7 Hz in the (**11a**) and J = 8.4 Hz (**11b**) were obtained, which are similar to those reported for related fused cyclopropanes. For examples, see: H. E. Zimmerman, L. C. Roberts, R. Arnold *J. Org. Chem.* **1977**, *42*, 621–629.