Organocatalysis

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Organocatalytic Synthesis of Highly Substituted Furfuryl Alcohols and Amines**

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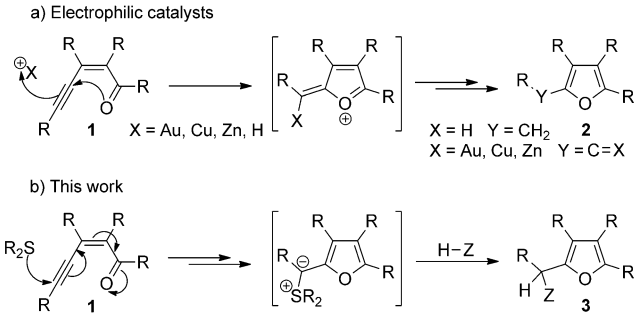
Substituted furans are present in many natural products,[1] bioactive compounds,[2] and functional materials.[3] Furans also serve as valuable building blocks for organic synthesis.[4] Driven by this prevalence, many methods have been developed for the synthesis of substituted furans.[5] In addition to traditional methods,[6] metal-mediated furan syntheses are becoming common. In particular, a variety of metals have been used to induce intramolecular carbonyl oxycyclization onto alkynes; electrophilic activation of alkynes has been demonstrated by using Lewis acidic complexes of copper[7] and zinc.[8] Additionally, gold-mediated furan syntheses have been reported;[9] these syntheses involve both intermolecular couplings,[10] and intramolecular cyclization of a range of 4- and 5-oxygenated alkynyl substrates.[11] Furthermore, gold- and silver-mediated cyclizations triggered by nucleophilic substrate activation have been reported.[12] These metal-mediated procedures are predated by reports of electrophilic activation of enynones by Brønsted acid (Scheme 1a, X = H).[13,14]



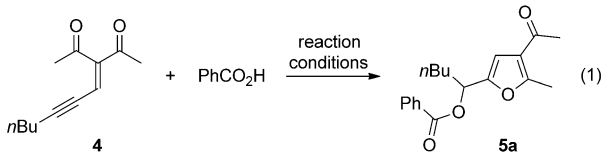
Scheme 1. Furan synthesis from carbonyl-conjugated enynes.

In contrast to metal-mediated processes, organocatalytic approaches to the construction of furans are scarce. Jørgensen and co-workers have reported an organocatalytic Feist–Benary synthesis,[15] but the complimentary approach, using nucleophilic activation of conjugated alkynylcarbonyl systems, is rare. Indeed, examples are limited to catalysis by Lewis basic phosphines. For example, Krische and co-workers have reported the triphenylphosphine-induced reductive condensation of γ-acyloxy butynoates to give furans.[16] Additionally, Kuroda et al. have developed a furan-forming reaction cascade that is initiated by the reaction of a stoichiometric amount of a phosphine with an enynone to give a phosphorus ylide, which is trapped by an aldehyde to give an α-alkenylfuran.[17] Inspired by this report of phosphine-based organocatalysis, we postulated that a similar cascade could be triggered by a thioether (Scheme 1b).[18] Sulfur-containing compounds have been shown to act as nucleophilic catalysts[19] and it seemed possible that a versatile sulfonium ylide could be generated when a sub-stoichiometric amount of a thioether is used.

The seminal experiment in our study involved the reaction of enynedione **4** with a stoichiometric amount of tetrahydrothiophene (THT) and an excess of benzoic acid [Table 1, Eq. (1)]. This reaction resulted in the formation of the furfuryl benzoate **5a** (Table 1, entry 1).

A screen of reaction conditions revealed that there was 50% conversion of the substrate into the benzoate **5a** after 24 h (Table 1, entry 1). The reaction also proceeded with

Table 1: Preliminary optimization studies.[a]



Entry	Catalyst	Loading [mol%]	Solvent (conc.)	*T* [°C]	Conv. at 24 h [%][b]
1	THT	100	$CDCl_3$ (0.1 M)	45	50
2	THT	50	$CDCl_3$ (0.1 M)	45	20
3	THT	10	$CDCl_3$ (0.1 M)	45	5
4	THT	10	$CDCl_3$ (1.0 M)	45	40
5	None	–	$CDCl_3$ (0.1 M)	45	0
6	DMAP	100	$CDCl_3$ (0.1 M)	45	decomp.[c]
7	DABCO	100	$CDCl_3$ (0.1 M)	45	decomp.[c]
8	PBu_3	100	$CDCl_3$ (0.1 M)	45	decomp.[c]
9	THT	10	CH_2Cl_2 (1.0 M)	reflux	60
10	THT	10	THF (1.0 M)	reflux	5
11	THT	10	PhMe (1.0 M)	reflux	60

[a] **4** (1.0 equiv), $PhCO_2H$ (1.1 equiv). [b] Determined by ^1H NMR analysis, and rounded to the nearest 5%. [c] Substrate **4** was consumed completely. DMAP = 4-dimethylaminopyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane, THT = tetrahydrothiophene.

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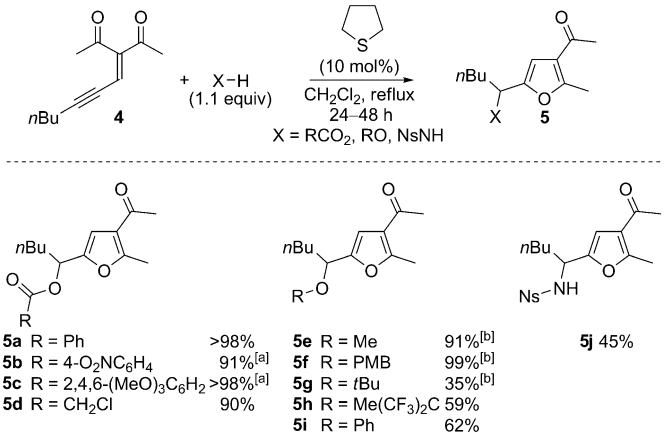
substoichiometric amounts of THT, although at a reduced rate (Table 1, entries 2, 3). Increasing the concentration of the reaction mixture was beneficial and the reaction proceeded at a reasonable rate with only 10 mol% of catalyst (Table 1, entry 4). The crucial role played by THT was demonstrated by the fact that the enynedione **4** failed to react in its absence (Table 1, entry 5). The efficacy of several alternative organocatalysts[17,19d] was investigated but consumption of starting material was observed without furan formation in all cases (Table 1, entries 6–8). The reaction proceeded in a variety of solvents and although it was low yielding when performed in THF (Table 1, entry 10), comparable rates of reaction were observed for reactions performed in [D]chloroform, dichloromethane (Table 1, entry 9), and toluene (Table 1, entry 11).

The results presented in Table 1 showed that the reaction is robust and operates under a variety of conditions and so the reaction was further examined to establish whether other nucleophiles could be used (Scheme 2). Electron-rich and electron-poor aryl carboxylic acids gave the furan products **5a** and **5b** in high yield, but reactions were slow unless the loading of THT was increased (50 mol%).



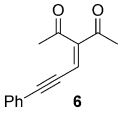
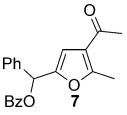
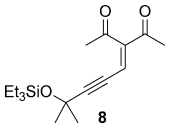
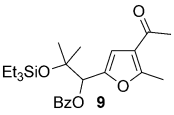
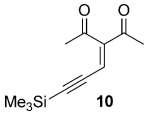
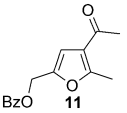
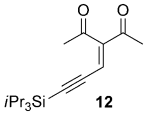
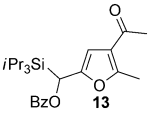
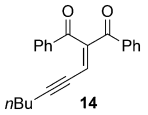
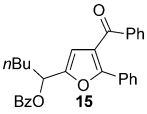
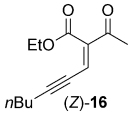
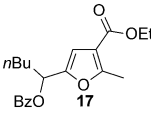
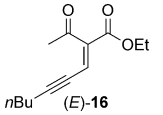
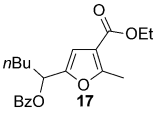
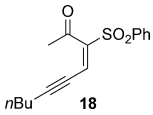
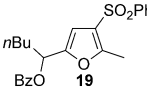
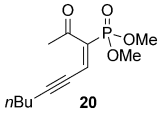
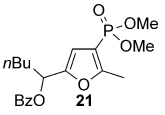
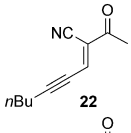
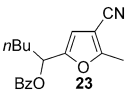
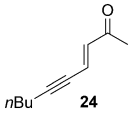
5a R = Ph >98%
5b R = 4-$O_2NC_6H_4$ 91%[a]
5c R = 2,4,6-$(MeO)_3C_6H_2$ >98%[a]
5d R = CH_2Cl 90%
5e R = Me 91%[b]
5f R = PMB 99%[b]
5g R = *t*Bu 35%[b]
5h R = $Me(CF_3)_2C$ 59%
5i R = Ph 62%
5j 45%

Scheme 2. Scope of nucleophile. Yields of the isolated products after chromatography. [a] 50 mol% of THT used. [b] 3.0 equiv of nucleophile was employed. PMB = *p*-methoxybenzyl; Ns = *p*-nitrobenzenesulfonyl.

A highly acidic nucleophile is not necessary and when the reaction was conducted in methanol, the methyl ether **5e** was the only product observed after 24 h. When a modest excess of methanol (3 equiv) was used, the *O*-methyl furfuryl alcohol **5e** was produced efficiently. The use of *p*-methoxybenzyl alcohol allowed for the formation of a protected α-hydroxyfuran **5f** in excellent yield. When bulkier *tert*-butyl alcohol was used this also led to the desired furan **5g** but with a lower yield. The use of fluorinated *tert*-butanol as nucleophile to give **5h** was more successful, a finding that suggests the pK_a of the acid is important. Phenol was also employed as the nucleophile in the furan-forming process (product **5i**). Finally, the use of *p*-nitrobenzenesulfonamide as nucleophile allowed incorporation of a protected amine to give **5j**.

The scope of electrophile was also examined (Table 2). The cyclization reaction proceeded in high yield with an aryl-substituted alkyne (Table 2, entry 1). High yields were obtained even when the substrate possessed a tetrasubstituted carbon center adjacent to the site of nucleophilic attack (Table 2, entry 2). The sterically congested silyl-substituted alkynes **10** and **12** also reacted to give furans (Table 2, entries 3 and 4). However, the trimethylsilyl-substituted enyne **10** underwent reaction to give the desilylated product **11** (Table 2, entry 3) whereas the triisopropylsilyl compound afforded furan **13**, in which the silicon substituent is retained

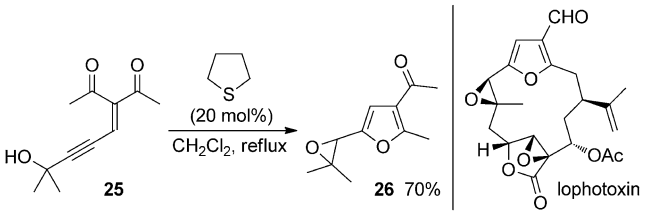
Table 2: Scope of electrophile.[a]

Entry	Electrophile	Product	Yield [%][b]
1	 **6**	 **7**	98
2	 **8**	 **9**	92
3	 **10**	 **11**	70
4	 **12**	 **13**	58[c]
5	 **14**	 **15**	89
6	 (*Z*)-**16**	 **17**	97[c]
7	 (*E*)-**16**	 **17**	–(60)[c,d]
8	 **18**	 **19**	> 98
9	 **20**	 **21**	65
10	 **22**	 **23**	63[c]
11	 **24**	–	no reaction[c]

[a] Substrate (1.0 equiv), $PhCO_2H$ (1.1 equiv), THT (10 mol%), 1 M in CH_2Cl_2, reflux, 18 h. [b] The yield of the isolated product after chromatography. [c] 50 mol% of THT was employed. [d] The value in brackets is the % conversion, measured by ^1H NMR spectroscopy at the time taken for complete consumption of substrate (*E*)-**16**. Bz = benzoyl.

(Table 2, entry 4). The phenyl-substituted substrate **14** reacted to give the furan **15** in excellent yield (Table 2, entry 5). The reaction was also performed on substrates in which one of the ketone carbonyl groups was replaced with another electron-withdrawing substituent. When the substrates (*E*)-**16**, **18**, **20**, and **22** (Table 2, entries 6, and 8–10) were used, the reaction afforded the corresponding furans **17**, **19**, **21**, and **23** in good to excellent yield. It is noteworthy that the ketoester (*Z*)-**16** displayed reduced reactivity in comparison to (*E*)-**16** (Table 2, entries 6 and 7). At the stage where reaction of (*E*)-**16** was complete, only 60% conversion was observed for (*Z*)-**16** and isomerization of the starting material was found. The reaction failed when substrate **24** was exposed to the reaction conditions (Table 2, entry 11).

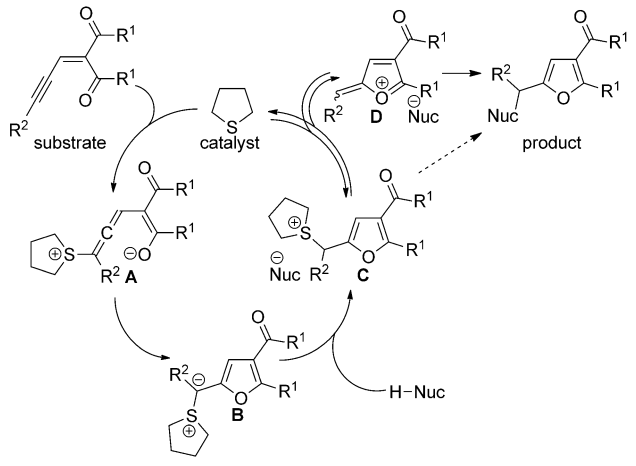
Treatment of substrate **25**, which contains a hydroxy group tethered to the electron-deficient enynedione, with THT resulted in a smooth reaction to deliver the epoxyfuran **26** in 70% yield (Scheme 3). Epoxyfurans can be unstable and so



Scheme 3. Synthesis of the epoxyfuran motif of lophotoxin.

the success of this reaction demonstrates the mild nature of the reaction conditions.[20] This result suggests a potential application of the reaction in target synthesis because the furan **26** is analogous to a key motif found in the neurotoxin lophotoxin and related marine furanocembranes.[21]

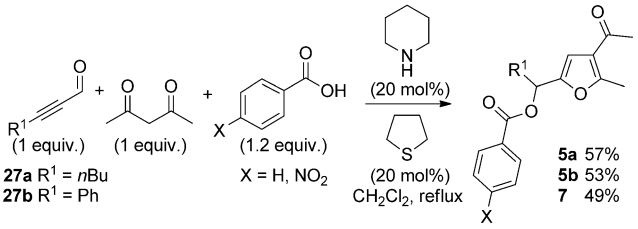
The proposed reaction mechanism commences with conjugate addition of THT to the alkyne (Scheme 4). The resulting enolate **A**[22] then cyclizes to form the furan **B**, bearing an adjacent sulfur ylide.[23] This ylide is sufficiently basic to deprotonate the acid to give the corresponding sulfonium ion **C** and the nucleophile. Rather than undergoing direct S_N2 reaction to form the observed product **5**, it is likely



Scheme 4. Proposed catalytic cycle.

that an S_N1 pathway is operative, releasing THT back into the catalytic cycle.[24,25] The resulting ion **D** is then captured by the nucleophile to generate the product.

The compatibility of THT with other organocatalytic processes was investigated (Scheme 5). Most of the substrates used herein were accessed by the Knoevenagel condensation



Scheme 5. Multicomponent domino synthesis of furfuryl benzoate **5a**.

of a 2-alkynal, a process that is promoted by a mixture of an alkylamine and carboxylic acid. We reasoned that the condensation reaction would be orthogonal to the furan-forming process and that they might be combined into a one-pot sequence.[26] When a mixture of aldehyde **27a** or **27b**, acetylacetone, and either benzoic or 4-nitrobenzoic acid was heated with piperidine and THT, the furfuryl benzoates **5a**, **5b**, and **7** were isolated in yields ranging from 49–57%, which are consistent with yields obtained when the reactions were performed separately. A slight excess of acid is required because it performs a dual role as a catalyst and a nucleophile. Remarkably, the furan-forming reaction tolerates the presence of water formed during Knoevenagel condensation.

In summary, a simple organocatalytic synthesis of substituted furans has been developed. The novel features of the procedure include the use of a simple thioether (THT) as the organocatalyst, the formation of a furan under neutral conditions rather than the anionic or acidic conditions employed in conventional syntheses, and the intermediacy of a versatile sulfonium ylide that has the potential to be intercepted directly by a variety of electrophiles instead of being protonated to give a sulfonium ion. The reaction proceeds with a wide range of substrates and nucleophiles to give highly decorated furans in good yield. The process is mild and can lead to the formation of a fragile, biologically-relevant epoxyfuran motif. The complementary nature of the THT catalysis with other organocatalyzed processes has allowed the reaction to be incorporated into a three-component domino sequence.

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Keywords: domino reactions · enynes · furans · organocatalysis · thioethers

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