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One-Pot Synthesis of 2-Methylfurans from 3-(Trimethylsilyl)propargyl Acetates Promoted by Trimethylsilyl Trifluoromethanesulfonate

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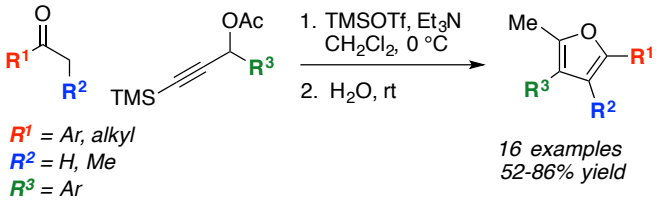
ABSTRACT

In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine, 3-(trimethylsilyl)propargyl carboxylates undergo a one-pot alkylation-cyclization-desilylation reaction with ketones to produce 2-methylfurans. Alkylation at 0 °C in methylene chloride, followed by acid-catalyzed cyclization at room temperature, provides the furans in 52-86% yield. Cyclization and desilylation appear to be promoted by triflic acid generated in situ from the exposure of the reaction mixture to water upon completion of the initial substitution reaction.

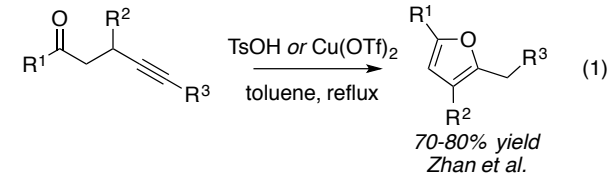


One-Pot Synthesis of 2-Methylfurans from 3-(Trimethylsilyl)propargyl Acetates Promoted by Trimethylsilyl Trifluoromethanesulfonate

*Danielle E. Sklar, Alex V. Helbling, Yiqi Liu, and C. Wade Downey,**

Keywords: furan synthesis, silyl triflate, one-pot reactions, cyclizations

Furans remain desirable synthetic targets due to the challenge of their construction and to their important medicinal properties,[1] as exemplified by the antitumor agent Lapatinib,[2] the ulcer drug Ranitidine,[3] and the 2,3,5-trisubstituted furan Roseophilin,[4] which exhibits activity against leukemia cell lines. Cyclization reactions to produce furans, however, generally require elevated temperatures to achieve high yields of the desired products.[5] Accordingly, the development of a convergent room-temperature furan synthesis a worthy goal. Our group was attracted to the potential of a strategy employed by Zhan and coworkers, which involves the cyclization of β-alkynylketones by heating in the presence of $Cu(OTf)_2$[6] or *p*-toluenesulfonic acid (eq 1).[7,8,9] Our recent success with the generation of similar β-alkynylketones through a one-pot enol silane formation-alkylation reaction promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf) (eq 2)[10] suggested that cyclization under similar conditions might be achieved. For reasons discussed below, we targeted the construction of 2-methylfurans, versatile synthons that can be easily alkylated [11] or oxidized [12] at the methyl position. We now report that 3-(trialklylsilyl)propargyl carboxylates react with ketones via a one-pot enol silane formation-alkylation-cyclization-desilylation sequence to provide 2-methyl-3,5-disubstituted furans at room temperature in the presence of TMSOTf and Et_3N.



During the course of our investigation of the TMSOTf-promoted propargylation reaction, triethylsilyl-substituted propargyl propionate **1a** reacted inconsistently under our reaction conditions, sometimes producing the expected β-alkynylketone, and other times undergoing cyclization to furan **2a** (eq 3). When β-alkynylketone **3** was resubjected to the reaction conditions, conversion to the furan was again inconsistent, and the product mixture was complicated further by the presence of 2-(triethylsilyl)methylfuran **4a**. After further experimentation, however, it was discovered that cyclization and desilylation were dependent on the presence of trace amounts of water; when β-alkynylketone **3** was treated

with TMSOTf and water followed by removal of the solvent in vacuo without workup, full conversion to the desired furan **2a** was observed (eq 4). Identical results were observed when substrate **3** was treated directly with HOTf.

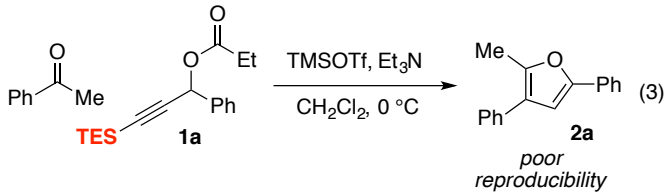
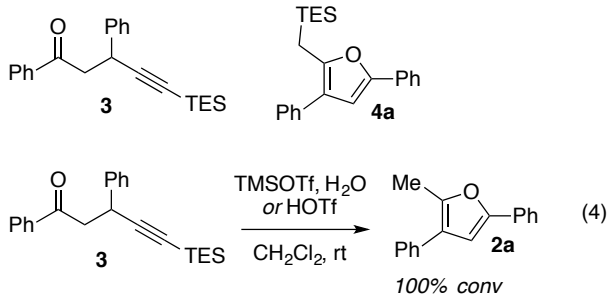
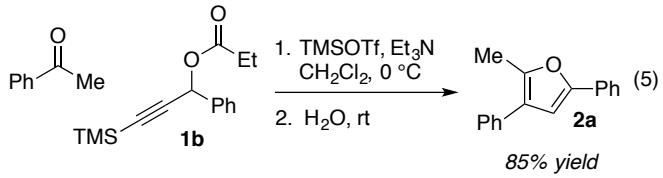


Figure 1. Intermediates observed during furan formation



In light of this discovery, the procedure for the one-pot generation of the furan directly from the starting ketone and propargyl propionate was modified to omit any workup other than removal of solvent, and high conversion to the 2-methylfuran was observed. Replacement of the triethylsilyl group at the 3 position in the substrate with the more readily available trimethylsilyl group did not hamper reactivity; employment of electrophile **1b** resulted in an 85% isolated yield of desired furan **2a** (eq 5).

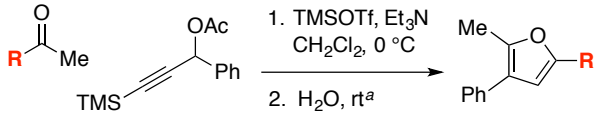


With the optimal reaction conditions established, the propionate leaving group on the propargyl carboxylate was replaced with the more common acetate, and a survey of ketones was conducted in order to determine the reaction scope of the nucleophile. As illustrated in Table 1, a wide range of methyl ketones provided 2-methylfurans upon coupling. A small drop in yield was observed for the acetate when compared with the propionate for an otherwise identical reaction (82% vs. 85% yield, entry 1). Given the prevalence and ease of synthesis of acetate esters, however, the acetate leaving group was selected for further studies.

While most aryl methyl ketones provided the 2-methylfurans in high yield when coupled with the propargyl acetate, more electron-rich and more hindered substrates appeared to be less reactive (entries 5-7). The reactions of the acetonaphthone isomers provided especially interesting results. In the case of 2-acetonaphthone, quantitative desilylation of the furan was not achieved, and the desired product was co-isolated with a 9% yield of the silylated

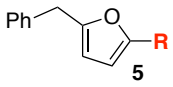
furan. In addition, both the 2-acetonaphthone reaction and the 1-acetonaphthone reaction generated small amounts of isomeric products, 2,5-disubstituted furans **5**. These byproducts likely arise from SN1' substitution of the propargyl acetate at the 3 position followed by ring closure.[13]

Table 1. Ketone scope



entry	R	product	yield (%)[b]
1	Ph	**2a**	82(85)[c]
2	4-(NO_2)Ph	**2b**	78
3	4-FPh	**2c**	83
4	4-BrPh	**2d**	81
5	4-MeOPh	**2e**	55
6	2-naphthyl	**2f**	49[d]
7	1-naphthyl	**2g**	66[e]
8	*t*-Bu	**2h**	85
9	cyclopropyl	**2i**	57
10	OEt	-	0
11	SPh	-	0

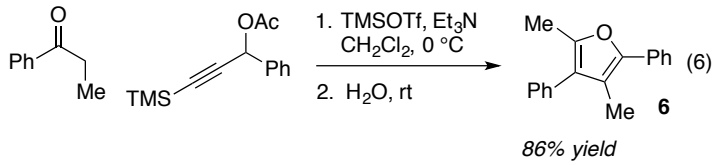
[a]1. Ketone (1.0 mmol), Et_3N (1.5 mmol), TMSOTf (1.3 mmol), CH_2Cl_2 (2.5 mL), r.t. 2. Propargyl acetate (1.1 mmol), CH_2Cl_2 (2.5 mL), 0 °C. 3. TMSOTf (0.55 mmol) 0 °C, 1 h. 4. H_2O (0.6 mmol), r.t., 0.5 h. [b]Isolated yield after chromatography. [c]Number in parentheses is the yield produced when propargyl acetate was replaced with propargyl propionate **1b**. [d]Yield corrected for the presence of silylated product (9% yield) and allene derivative **5** (5% yield) in the product mixture. [e]Yield corrected for the presence of and allene derivative **5** (4% yield) in the product mixture.



5

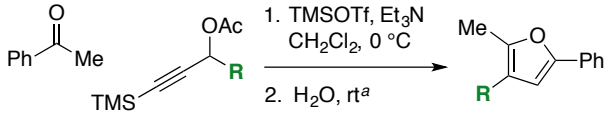
R = 1-naphthyl, 2-naphthyl

Expansion of the reaction scope to include alkyl-alkyl ketones provided additional successful examples. Pinacolone reacted in high yield to provide the *t*-Bu-substituted furan, while cyclopropyl methyl ketone afforded a more moderate yield of the derived bicyclic compound (entries 8-9). The scope was not limited to methyl ketones. When propiophenone was chosen as the ketone reactant, the ketone and propargyl acetate reacted to provide the desired ketone in 86% isolated yield (eq 6). Other carbonyl compounds, however, were ineffective. Both thioesters, which were viable substrates in our previous alkylation study, and esters failed in this instance to provide products in either cyclized or uncyclized form.[14]



Next, application of this one-pot, room-temperature method for the synthesis of 2-methylfurans was expanded through variation of the propargyl acetate. Although 1-alkylpropargyl acetates appeared to be unreactive under our conditions, presumably because of slow ionization, several 1-arylpropargyl acetates provided the desired furans in high yield when coupled with acetophenone (Table 2). Although the electron-poor 4-nitro- and 4-trifluoromethyl-substituted substrates did not provide products, failing to react even at reflux, propargyl acetates bearing halogen-substituted aryl rings were model reaction partners (entries 3-5), and more electron-rich aromatics reacted successfully as well (entries 6-7). The failure of the electron-poor derivatives to react can be attributed to slow ionization to form the requisite propargyl cation, which would be destabilized by the electron-withdrawing substituent. When a 1-heteroaryl propargyl acetate was employed, however, the reaction was again successful (entry 8), although variation to the cinnamyl-substituted substrate led only to rapid decomposition of the substrate (entry 9).

Table 2. Scope of propargyl acetate



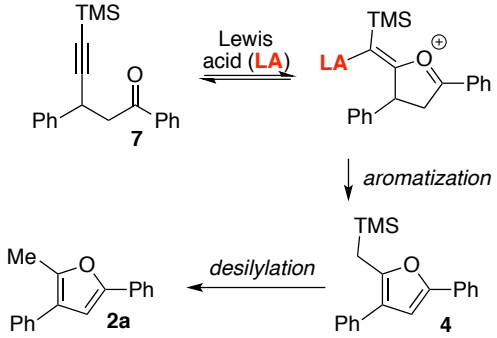
entry	R	product	yield (%)[b]
1	4-NO_2	-	0
2	4-CF_3	-	0
3	4-FPh	**2j**	85
4	4-ClPh	**2k**	83
5	4-BrPh	**2l**	83
6	4-MeOPh	**2m**	84
7	2-naphthyl	**2n**	86
8	2-thienyl	**2o**	62
9	cinnamyl	-	0

[a]1. Ketone (1.0 mmol), Et_3N (1.5 mmol), TMSOTf (1.3 mmol), CH_2Cl_2 (2.5 mL), r.t. 2. Propargyl acetate (1.1 mmol), CH_2Cl_2 (2.5 mL), 0 °C. 3. TMSOTf (0.55 mmol) 0 °C, 1 h. 4. H_2O (0.6 mmol), r.t., 0.5 h. [b]Isolated yield after chromatography.

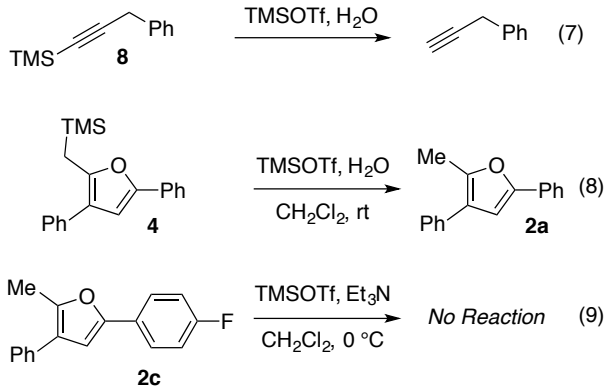
A working hypothesis for the mechanism of the one-pot furan synthesis is illustrated in Figure 2. The generation of substitution products **7** under very similar conditions has already been established, as has their conversion under slightly modified reaction conditions to furan **2a**. We propose that the presence of the terminal silyl group serves to increase the electron density, and thus the Lewis basicity, of the alkynyl residue, accelerating its coordination to Lewis acids present in the reaction mixture. These Lewis acids may include additional TMSOTf, which is present in excess, or HOTf generated in situ through the interaction of TMSOTf with added water. Cyclization and

thermodynamically driven aromatization followed by acid-promoted desilylation then yield the final furan.

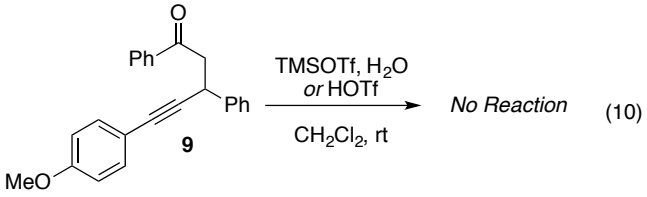
Figure 2. Proposed mechanistic scheme for furan generation

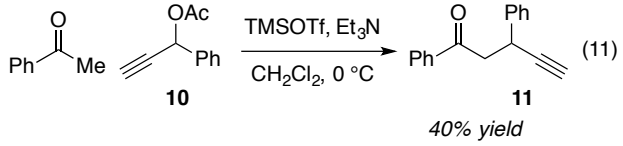


A series of experiments provided support for this proposed sequence of events. First, the possibility that cyclization might occur via a diketone intermediate, rather than direct attack on an activated alkyne, was addressed. The requisite diketone might form under the reaction conditions by HOTf-promoted hydration to produce a carbonyl, which could serve as an electrophilic center to accelerate ring closure as observed by Montgomery and coworkers under forcing conditions.[15] To test this hypothesis, model silylalkyne **8** was synthesized via literature precedent[16] and subjected to TMSOTf and water in methylene chloride for 2 h (eq 7), conditions analogous to our cyclization conditions. No ketone was observed in this experiment, which produced a mixture of only the starting alkyne and its desilylated analog. These results suggest that a diketone is an unlikely intermediate in the present furan synthesis. In contrast, evidence did support the intermediacy of silylated furan **4**. As stated above, silylfuran **4** was frequently observed in product mixtures during optimization experiments, and in the case of furan **2f**, the silylated analog could not be fully removed from the product mixture. In most cases, however, when silylfuran **4** and its analogs were resubmitted to a solution of TMSOTf and water in methylene chloride, complete conversion to the desired furan occurred (eq 8), an observation consistent with the silylfuran's role as intermediate in the reaction mechanism. Moreover, when furan **2c** was resubmitted to the reaction conditions, no silylation was observed (eq 9), which suggests that any silylated furans present in the original reaction mixtures do *not* derive from the final products. These place the silylfurans as intermediates rather than byproducts in the reaction mechanism.



The role of the electropositive 3-trialkylsilyl substituent as an accelerant in the cyclization step was probed in two experiments. To test whether or not another electron-rich substituent at the 3-position might provide similar results, β-alkynylketone **9**, bearing an electron-rich *p*-anisyl group, was subjected in parallel to two proven sets of cyclization conditions (HOTf or TMSOTf/H_2O). In neither case were cyclized products observed, although some decomposition of the substrate did occur (eq 10). The complete removal of substituents from the 3-position provided evidence for both the role of the trialkylsilyl group and the position of the desilylation event in the mechanistic sequence. Because Nishizawa and coworkers have noted that terminal alkynes undergo a mercury-catalyzed cyclization-aromatization process analogous to the one presented here,[17] it was necessary to determine more definitively if desilylation might precede cyclization for the current reaction, especially given the desilylation of alkyne **8** under similar conditions (eq 7).[18] When acetophenone was treated with desilylated propargyl acetate **10**, however, no conversion the furan was observed, although a modest yield of substitution product **11** was recovered (eq 11). These results provide some further evidence for the necessity of a terminally silylated substrate in the desired one-pot process, and suggest that desilylation likely occurs subsequent to cyclization.





In summary, we have demonstrated that TMSOTf and Et_3N promote a one-pot furan synthesis from 3-(trialkylsilyl)propargyl acetates and simple ketones. The cyclization occurs conveniently at room temperature to produce tri- and tetra-substituted 2-methylfurans. This cyclization-aromatization-desilylation reaction requires a terminally silylated alkyne substrate for successful completion, and appears to be mediated by HOTf that forms in situ from the interaction of TMSOTf with water.

ACKNOWLEDGMENTS

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upon work supported by the National Science Foundation under Grant No. (CHE-1726291).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxx. These data include MOL files and InChiKeys of the most important compounds described in this article.

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[14] Although it is possible that cyclization occurs for these substrates and the resulting electron-rich furans decompose under the reaction conditions, we have observed no direct evidence to support this hypothesis.

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