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# Rapid and Facile Synthesis of Highly Substituted Furans

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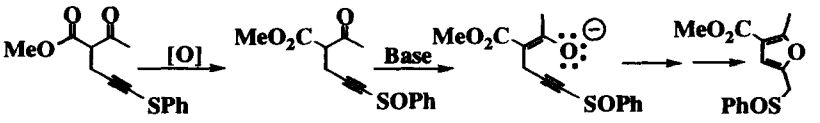
**Abstract:** A short and efficient synthesis of highly substituted furans has been accomplished. The method is amenable for the production of 2,5-di, 2,3,5-tri and 2,3,4,5-tetrasubstituted furan compounds containing multiple functionalities. © 1997 Elsevier Science Ltd.

Furans are ubiquitous compounds. They proliferate throughout nature in a wide variety of commercially important compounds; including pharmaceuticals (anti-inflammatory properties), flavour and fragrance compounds.[1,2] Furans also play an important role as intermediates in many synthetic pathways, primarily because they react as a special class of vinyl ethers[3] or as dienophiles in the Diels-Alder reaction.[4] It is due to the aforementioned utility of furans, along with the considerable synthetic challenge of many furan-containing natural products, that many methods have been devised for the syntheses of these derivatives. These include modification of commercially available furans,[5] cyclodehydration of saturated open chain 1,4-diketones,[6] Diels-Alder-retro-Diels-Alder strategies with 4-phenyloxazoles and acetylenes,[7] cyclization of radicals and carbenes,[8] metal catalyzed cyclization of alkenyl alcohols,[9] base induced cyclization of allenyl alcohols and epoxides,[10] as well as many others.[11]

We first became interested in substituted furans during the synthesis of alkynyl sulfones and sulfoxides,[12] where it was realized that upon the oxidation of acetylenic sulfide none of the expected alkynyl sulfoxide or sulfone was obtained, but instead, the initially oxidized product underwent *in situ* cyclization and isomerization to the trisubstituted furan, equation 1. The facility and expeditiousness of this transformation, presumably due to the presence of both the enolizable β-dicarbonyl functionality and the electron deficient alkyne, prompted us to investigate the boundaries of this methodology.




(1)

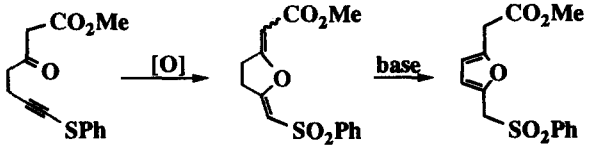
The substrates[13] shown in Table 1 were prepared to address the following questions: a) was the method extendible to other acetoacetates, β-dicarbonyl or similar derivatives; b) could the sulfoxide electron withdrawing group on the alkyne be exchanged for other electron withdrawing functional groups; c) would it be

possible for cyclizations to take place with the alkynyl chain in a position other than α to both carbonyls; and d) would a wide variety of functionalized furans be accessible, including tetrasubstituted ones?

Inspection of entries 1 and 6-8 demonstrates that a variety of β-dicarbonyl or similar derivatives can be used as the motif for generating the enolizable portion of the molecule, and that cyclization and aromatization proceed in respectable overall yields, 45%-85%, using 10 mol % of benzyltrimethylammonium methoxide (BTMA). Of the readily enolizable substrates investigated, it was our experience that β-keto esters were the best; we routinely obtained yields in excess of 70% for the complete sequence (alkylation--->aromatization, entries 1 and 3).

A diversity of functionality can be utilized on the alkyne to induce cyclization. These range from electron withdrawing groups such as aldehydes (entry 2), ketones (entry 4), esters (entry 3) and sulfones (entry 1), to simple halides (entry 5), which undoubtedly proceeds *via* an initial $S_N2'$ reaction to produce an allene, and then undergoes isomerization to generate the exocyclic olefin. It should be mentioned that the use of an aldehyde to create an electron deficient alkyne is somewhat capricious, entry 2. In order to isolate any of the aromatic compound the aldehyde had to be immediately reduced or else undesired side reactions totally consumed the product. That aside, a medley of 2,3,5-trisubstituted furans containing a number of different functional groups with different oxidation states can be easily obtained.

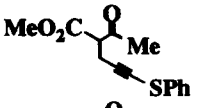
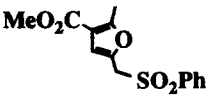
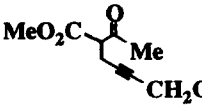
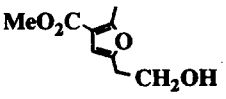
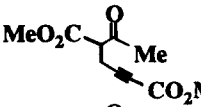
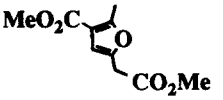
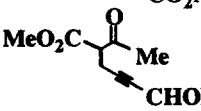
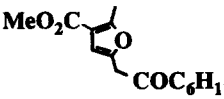
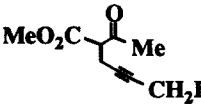
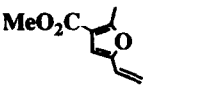
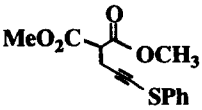
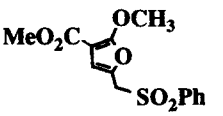
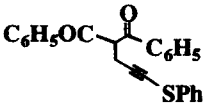
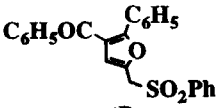
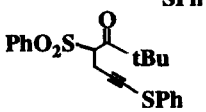
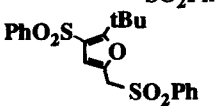
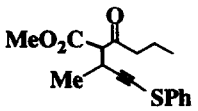
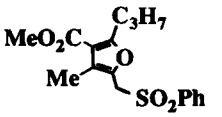
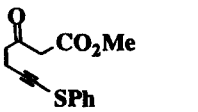
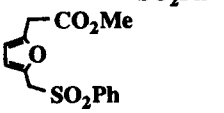
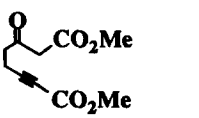
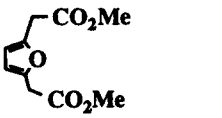
With the success of this strategy for the production of 2,3,5-trisubstituted furans, two compounds were synthesized to probe the utility of the method for the generation of 2,5-disubstituted furans. A potential difficulty was that aromatization to the furan may prove difficult considering that after initial cyclization the conjugated alkenes would have to be deconjugated, thus destroying the stability of the vinylogous ester, equation 2. As shown in Table 1 (entries 10 and 11) these fears proved unwarranted as the two substrates smoothly underwent the reaction sequence to generate the substituted furans in good yields. Although not pursued, presumably other β-dicarbonyl compounds of similar structure would behave analogously.




(2)

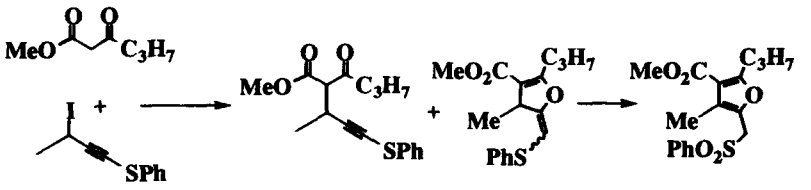
Finally, the possibility of generating tetrasubstituted furans was investigated (entry 9). Although ultimately successful, it was noted that attempted production of substrates like that used in entry 9, *via* standard alkylation procedures, usually generated a mixture of the acyclic and cyclic products (5:1 acyclic:cyclic), equation 3. The ratio of these two products could be varied such that the cyclized product was the major compound simply by increasing the temperature (from 40°C to 65°C) and the time (from 12 hr. to 24 hr.) of the substitution reaction. However, the longer the reaction proceeded at elevated temperatures the lower the yield. As a result, for compounds of this type the alkylation reactions were usually run at 40°C in THF for 12 hours, and then the crude reaction product was directly oxidized and aromatized before attempting any purifications. The reason for substrates like that in entry 9 to undergo such facile cyclization is not obvious. Although cyclization of anions onto thio- and alkoxyacetylenes have been demonstrated, stabilized anions like malonates or acetoacetates do not effectively participate in this reaction,[14] as evidenced in our other experiments, entries 1,

**Table 1: Furan synthesis initiated by various electron withdrawing groups on the alkyne.**

| Entry | Carbonyls | Conditions | Product | % Isolated Yield |
|---|---|---|---|---|
| 1 |  | a |  | 85 |
| 2 |  | b |  | 45 |
| 3 |  | c |  | 91 |
| 4 |  | d |  | 65 |
| 5 |  | e |  | 88 |
| 6 |  | a |  | 71 |
| 7 |  | a |  | 46 |
| 8 |  | a |  | 45 |
| 9 |  | a |  | 74 |
| 10 |  | a |  | 83 |
| 11 |  | c |  | 72 |

**Conditions:** **(a)** 1. mCPBA (2.2 eq), $CH_2Cl_2$, 2. BTMA (10 mol %), MeOH, rt, 12 hr.; **(b)** 1. PDC, $CH_2Cl_2$, 2. BTMA (3 mol %), MeOH, 4 hr., 3. $NaBH_4$, EtOH; **(c)** BTMA (10 mol %), MeOH, rt, 12 hr.; **(d)** 1. Jones Ox., 2. BTMA (10 mol %), MeOH, rt, 12 hr.; **(e)** BTMA (1.05 eq), MeOH, rt, 12 hr.

6, 7 and 8. Although some unfavourable nonbonding interactions may exist, simple molecular modeling does not reveal any interactions that are untoward that could explain this remarkable result. The exact reasons or factors responsible for this phenomenon will have to await further experimentation. Regardless of this, tetrasubstituted furans can be efficiently and rapidly generated from simple starting materials; a fact which we have recently exploited in the total synthesis of calicogorgin A.[15]




(3)

In conclusion, a mild and efficient method for the formation of di-, tri- and tetrasubstituted furans by intramolecular Michael-type or $S_N2'$ reaction of readily enolizable substrates on alkynyl esters, sulfones, aldehydes, ketones or halides has been developed. This strategy is comparable to existing literature methods with yields ranging from 45-91% and is characterized by the simplicity of starting materials, the technical ease of the reaction sequence, and the range of functional groups obtainable in the final furan compounds. Further studies into the use of alkynes for the synthesis of substituted furans will be communicated in the near future.

**Acknowledgments:** We gratefully thank NSERC Canada and the University of New Brunswick for financial support.

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13. The substrates used in this study were prepared by the following procedures: **entries 1-6** ( 1. carbonyl, THF, NaH, alkynyl halide; 2. NaH, nBuLi, THF, 1 eq. of $E^+$ [PhSSPh, $CH_2O$, $OC(OMe)_2$, $C_6H_{11}CHO$); 3. for entry 5: carbonyl from entry 2, NBS, $PPh_3$, $CH_2Cl_2$; **entries 7-8** (carbonyl, DMF, tetrabutylammonium methoxide, alkynyl halide[15]); **entry 9** (see ref. 15); **entry 10** (1. NaH, nBuLi, THF[16]; 2. 1-iodo-3-thiophenyl-2-propyne[15]; **entry 11** (1. NaH, nBuLi, THF, propargyl bromide; 2. NaH, nBuLi, $ClCO_2Me$, THF). All the compounds, both starting substrates and products, were characterized by $^1H$ and $^{13}C$ NMR, IR and HREIMS or FABMS.
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