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Magnesium mediated carbometallation of propargyl alcohols: direct routes to furans and furanones

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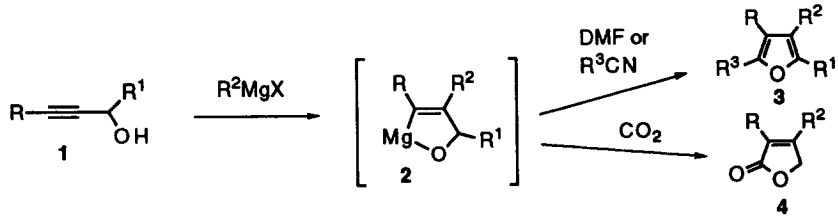
Abstract

The addition of vinyl and aryl Grignard reagents to propargyl alcohols for the direct synthesis of furans and butenolides from a one pot reaction is described. These products arise from a putative magnesium chelate intermediate **2** upon reaction with various electrophiles. This chelate was also generated in situ from alkynyl lithium addition to aldehydes followed by magnesium exchange and Grignard addition. Thus, the complete substitution pattern for the furan ring may be controlled, as desired, through the judicious choice of substrates and reagents.

Keywords: furan; furanone; butenolide; magnesium; propargyl.

In the preceeding Communication we have described the direct addition of vinyl and related Grignard reagents to propargyl alcohols **1** to generate the intermediate magnesium chelate **2** (or a closely related species) followed by reaction with aldehydes for the direct synthesis of diene–diols and enediynes.[1] We have extended these investigations and wish to report the versatile combinations which permit the direct synthesis of substituted furans (**3**) by a novel method as well as 2(5*H*)-furanones (butenolides) (**4**) depending upon the electrophiles selected (Scheme 1).



Scheme 1. Magnesium mediated carbometallation of propargyl alcohols

Furans comprise an important class of oxygen heterocycles. They have been isolated from a broad cross section of natural sources and have been employed both as key synthetic intermediates and as

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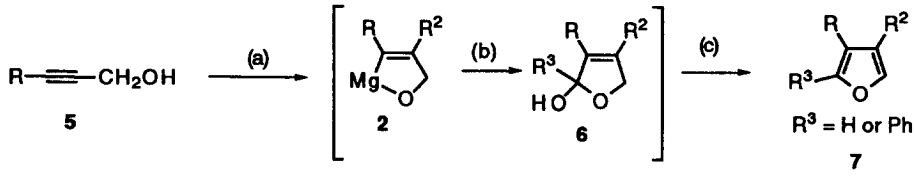
synthetic targets in their own right.[2] Consequently, new preparative routes continue to be developed.[3] However, few of these methods allow the synthesis of tetrasubstituted furans.[4] Following the Grignard based carbometallation protocol developed previously, substituted furans **7** may be synthesized directly upon reaction of **2**, derived from **5**, by reaction with dimethylformamide (DMF) followed by acidification without isolation of the intermediate hemiacetal **6** (Scheme 2).



Scheme 2. Route to trisubstituted furans. (a) 3.2 equiv. R^2MgCl, C_6H_{12}, 80°C, 19 h; (b) DMF or R^3CN, 0°C, 0.5 h, 22°C; (c) *p*-TsOH, C_6H_6, 21°C, 30–60 min

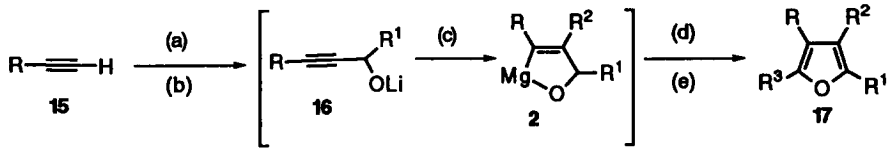
Alternatively, condensation with aryl nitriles in place of DMF allowed the direct synthesis of more highly substituted furans in which the substitution pattern at the 2-, 3-, and 4-positions may be controlled systematically. Table 1 illustrates various combinations with either DMF or benzonitrile. Unfortunately, the acidic conditions required for the elimination of water also induced decomposition and reduced yields for the more labile compounds **11**, **13** and **14**. These vinyl furan systems contain useful functionality for the construction of more complex skeletons via a double Diels–Alder strategy and may also be used as monomers.

Table 1
Synthesis of substituted furans

Entry	Reactants (DMF)	Furan	Entry	Reactants (PhCN)	Furan
a	Ph—≡—CH_2OH, PhMgCl	**8** 92%	e	Ph—≡—CH_2OH, CH_2=CHMgCl	**12** 62%
b	Ph—≡—CH_2OH, CH_2=CHMgCl	**9** 72%	f	TMS—≡—CH_2OH, PhMgCl	**13** 41%
c	TMS—≡—CH_2OH, CH_2=CHMgCl	**10** 58%	g	TMS—≡—CH_2OH, CH_2=CHMgCl	**14** 28%
d	TMS—≡—CH_2OH, PhMgCl	**11** 46%			

The versatility and scope of this furan synthesis was extended by the in situ generation of the intermediate chelate **2** via lithium–magnesium transmetallation. Thus, modification of the standard

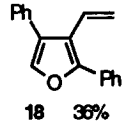
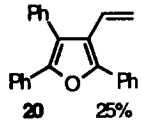
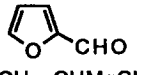
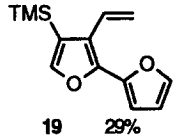
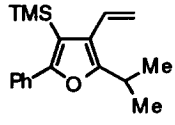
protocol permitted the introduction of substituents at the eventual C-5 position of the furan, to allow independent control of the substituent at the remaining position. Addition of the alkynyl lithium salt derived from **15** to an aldehyde afforded the lithium alkoxide **16** as illustrated in Scheme 3. This was followed by transmetallation with vinyl magnesium chloride and Grignard addition to form the chelate **2** which could then be reacted with either DMF or a nitrile derivative. This protocol generated a family of furans **17** in which the substitution pattern at all four positions could be predetermined.



Scheme 3. Alkynyllithium route to furans. (a) *n*-BuLi; (b) R^1CHO; (c) 3.2 equiv. R^2MgCl, C_6H_{12}, 80°C, 19 h; (d) DMF or R^3CN; (e) *p*-TsOH, C_6H_6, 21°C, 30–60 min

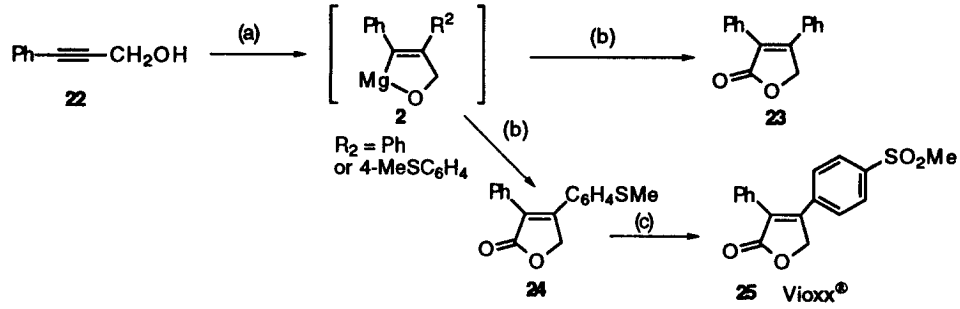
Table 2 lists various examples generated in this fashion including the 2,2′-bis-furan system **19**. Current routes to related bis-furan systems are usually accompanied by a few percent of the parent furan.[5] Thus, depending upon the substrate–reagent–reactant combination selected above, a large number of substituted furan systems may be prepared.

Table 2
Synthesis of tetrasubstituted furans

Entry	Reactants (DMF)	Furan	Entry	Reactants (PhCN)	Furan
a	Ph—≡—H PhCHO CH_2=CHMgCl	 **18** 36%	c	Ph—≡—H PhCHO CH_2=CHMgCl	 **20** 25%
b	TMS—≡—H  CH_2=CHMgCl	 **19** 29%	d	TMS—≡—H *i*-PrCHO CH_2=CHMgCl	 **21** 28%

Early examples of dialkyl butenolides derived from the condensation of species related to **2** with carbon dioxide have been reported,[6] and other methods are available.[7] However, in view of the challenge and medicinal interest[8] in preparing 3,4-diaryl-2(5*H*)-furanones such as 3,4-diphenylbutenolide (**23**), this aspect has also been examined. The lactone **23** was synthesized by the magnesium mediated carbometallation of phenylpropargyl alcohol (**22**) with phenylmagnesium chloride to form the chelate **2** followed by exposure to carbon dioxide (52% yield). Modification of this protocol in which **22** was reacted directly with 4-thiomethylphenylmagnesium chloride and the reaction quenched with carbon dioxide afforded **24**. Oxidation of **24** with *m*-chloroperoxybenzoic acid generated the sulphone **25** in quantitative yield. As illustrated in Scheme 4, this butenolide, the new Merck anti-inflammatory drug Vioxx®, may be synthesized in a facile manner using this method.

In summary, the magnesium mediated carbometallation protocols described above provides direct access to various oxygen heterocycles that may be employed for a variety of synthetic objectives.[9] Although in some cases the yields are modest, this short route to multisubstituted furans and 3,4-disubstituted



Scheme 4. A direct route to furanones including Vioxx® (**25**). (a) 3.2 equiv. PhMgCl or 4-$MeSC_6H_4MgCl$, C_6H_{12}, 80°C, 19 h; (b) CO_2; (c) *m*-CPBA, 0–21°C, 99%

butenolides in a controlled fashion is very useful. Thus, depending upon the substrate–reagent–reactant combination selected, a large number of compounds may be synthesized. In addition, the ease with which these compounds are prepared in one synthetic step renders this sequence attractive for the use of these building blocks for more complex targets. These investigations will be reported in due course.

Acknowledgements

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9. General procedure for the magnesium mediated carbometallation of propargyl alcohols to furans: Phenylmagnesium chloride (3.7 mL, 1.87 M in THF, 6.7 mmol) was added to a solution of 3-phenyl-2-propyn-1-ol (0.28 g, 2.1 mmol) in cyclohexane (4.1 mL) at 22°C. The solution was refluxed for 19 h. The solution was cooled to 0°C and *N,N*-dimethylformamide (0.53 mL, 6.7 mmol) was added. The mixture was stirred for 5 min at 0°C and refluxed for 3 h. Standard workup yielded the crude lactol which was immediately dissolved in benzene and treated with a catalytic amount of *p*-toluenesulfonic acid and stirred at 22°C for 2 h. The reaction was neutralized with saturated aqueous sodium bicarbonate, extracted with ether (3×10 mL), dried, concentrated, and chromatographed (20:1 to 12:1 petroleum ether:ether) to afford 3,4-diphenylfuran (**10**) as a white solid (0.42 g, 91%); mp 108–110°C; ^1H NMR δ 7.00–7.06 (m, 6H), 7.17–7.20 (m, 4H), 7.26 (s, 2H); ^{13}C NMR δ 126.4, 127.2, 128.7, 128.9, 132.6, 141.1; IR (NaCl) 1135, 803, 757, 696; MS (M^+) calcd 220.0889; obsd 220.0894. Anal. calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.24; H, 5.37.