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A Convenient Preparation of 3-Substituted Furans: Synthesis of Perillene and Dendrolasin

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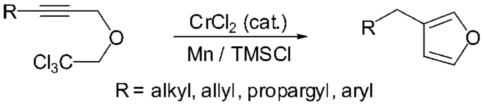
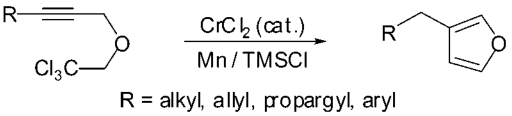
ABSTRACT



A variety of 3-substituted furans, including the natural products perillene and dendrolasin, are obtained in good yield via reductive annulation of 1,1,1-trichloroethyl propargyl ethers using catalytic Cr(II) regenerated by Mn/TMSCl.

Furans are common subunits in pharmaceuticals,[1] natural products,[2] fragrances,[3] and flavors.[4] They have also found utility as synthetic intermediates or synthons for numerous functional groups, inter alia, carboxylic acids, β-keto-esters, and aromatics.[5] While electrophilic aromatic substitution or metalation[6] of furans permit ready functionalization at C(2)/(5), these methods are not generally applicable to the preparation of C(3)-substituted furans. The latter are typically obtained by elaboration of an existing C(3)-substituent[7] or accessed from acyclic precursors via multistep sequences.[8] In continuation of our exploration of the chemistry of organochromium reagents,[9] we describe herein a convenient synthesis of C(3)-substituted furan by reductive annulation of 1,1,1-trichloroethyl propargyl ethers[10] mediated by catalytic Cr(II) coupled to a Mn/TMSCl regeneration system (eq 1).[11]



(eq 1)

To study the efficacy of the annulation, a representative panel of 1,1,1-trichloroalkynes was prepared by alkylation of 2,2,2-trichloroethanol with various propargyl bromides at

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(7) Mandai, T.; Takeshita, M.; Mori, K.; Kawada, M.; Otera, J. *Chem. Lett.* **1983**, 1909−1910.

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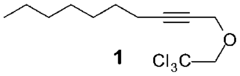
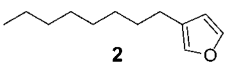
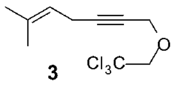
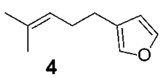
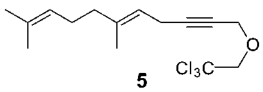
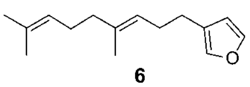
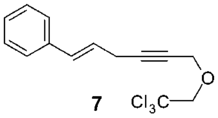
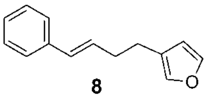
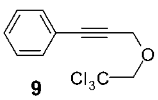
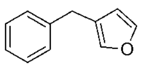
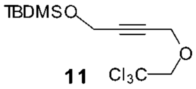
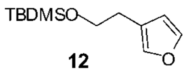
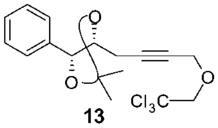
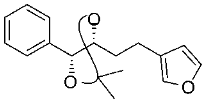
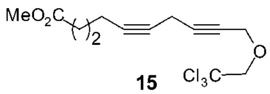
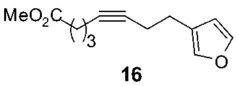
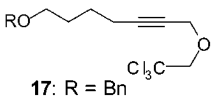
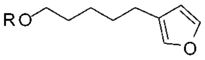
room temperature in the presence of NaOH/n-Bu_4NI in CH_2Cl_2.[12] Stirring the structurally simplest of these, **1**, with stoichiometric (4−6 equiv) $CrCl_2$ proved disappointing and never generated more than a 30% yield of furan **2**, regardless of solvent or temperature, with the remaining material balance being principally *Z*-chloroenol ether **30**. In stark contrast, **2** was obtained[13] in good yield (Table 1, entry 1) by warming a THF solution of **1** with a catalytic amount of $CrCl_2$, or more conveniently $CrCl_3$, coupled to a Mn powder/TMSCl regeneration system as prescribed by Fürstner.[14] Other solvents, e.g., HMPA, DMF, CH_2Cl_2, Et_2O, *p*-dioxane, and EtOAc, were less satisfactory. Notably, the corresponding tribromoethyl ether led to a complex product mixture containing little, if any, **2**.

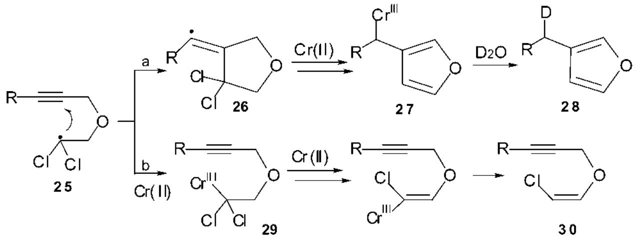
Table 1. Synthesis of 3-Substituted Furans

entry	trichloro-alkyne	furan	yield (%)
1	 **1**	 **2**	80
2	 **3**	 **4**	79
3	 **5**	 **6**	82
4	 **7**	 **8**	85
5	 **9**	 **10**	70[a]
6	 **11**	 **12**	20
7	 **13**	 **14**	78
8	 **15**	 **16**	87
			
9	**17**: R = Bn	**18**: R = Bn	76
10	**19**: R = Ac	**20**: R = Ac	82
11	**21**: R = TBDPS	**22**: R = TBDPS	81
12	**23**: R = H	**24**: R = H	85

[a] Six equivalents of $CrCl_2$ at 60 °C for 12 h.

Likewise, the naturally occurring[15] furanyl terpenoids perillene (**4**) and dendrolasin (**6**) were synthesized in a single step from isoprenoids **3** and **5** (entries 2 and 3, respectively) using catalytic $CrCl_2$. No olefin isomerization or reduction was observed during the transformation of styrene **7** to **8** (entry 4). Phenylacetylene **9**, on the other hand, was consumed under the standard catalytic conditions but afforded a poor yield (~20%) of **10**. However, the reaction efficiency was significantly improved using 6 equiv of $CrCl_2$ at 60 °C for 12 h and furnished **10** in 70% yield (entry 5). The presence of heteroatoms or leaving groups adjacent to the distal side of the acetylene resulted in low yields, for example, **11** to **12** (entry 6), although β-functionality was well tolerated (**13** to **14**, entry 7). The reaction conditions proved compatible with most other common functional groups as well, inter alia, methyl ester **15**, benzyl ether **17**, acetate **19**, silyloxy **21**, and free alcohol **23** which gave rise to 3-substituted furans **16** (entry 8), **18** (entry 9), **20** (entry 10), **22** (entry 11), and **24** (entry 12), respectively. A mechanistic interpretation of the preceding observations is summarized in Scheme 1. One electron transfer[16] from Cr(II) to the trichloroalkyne substrate with concomitant loss of chloride spawns the key radical intermediate **25** which undergoes cyclization[17] to give vinylchromium **26** under catalytic Cr(II) conditions (pathway a). Further transmetalation and aromatization lead to furan **27**. The latter was inferred by quenching with D_2O, which resulted in **28**, incorporating one atom of deuterium. Alternatively, in the presence of high concentrations of Cr(II), i.e., stoichiometric conditions, reduction of **25** to **29** is competitive (pathway b) and *Z*-chloroenol ether **30** is formed as previously described.[9a] Control experiments demonstrated that both Mn and TMSCl

Scheme 1



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[10] Multistep synthesis of 3-substituted furans using 1,1,1-trichloroethyl allyl ethers: Ram, R. N.; Charles, I. *Chem. Commun.* **1999**, 2267−2268.

[11] $CrCl_2$-based synthesis of 2,5-disubstituted furans: Takai, K.; Morita, R.; Sakamoto, S. *Synlett* **2001**, 1614−1616.

[12] Morimoto, T.; Sekiya, M. *Synthesis* **1981**, 308−310.

[13] **General procedure:** 1,1,1-Trichloroethyl propargyl ether (1 mmol) in THF (2 mL) is added to a stirring, room-temperature suspension of anhydrous $CrCl_3$ (15 mol %), Mn powder (4 mmol), and freshly distilled TMSCl (4 mmol) in THF (8 mL) under argon. After complete addition, the reaction mixture was heated at 60 °C. After 12−15 h, the reaction mixture was cooled to ambient, quenched with an equal volume of water, and extracted thrice with ether. The combined ethereal extracts were evaporated in vacuo and the residue was purified by SiO_2 chromatography to give 3-substituted furans in the indicated yields (Table 1).

[14] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349−12357.

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[16] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.

[17] Review of heterocyclic syntheses via radical cyclization: Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885−29.

are need for the catalytic procedure to succeed. However, the role of the TMSCl is obscure in this instance, but is not a source of HCl as proposed[11] in other systems since exogenously added acid was detrimental to the yield.

In summary, we report a convenient, high-yield synthesis of 3-substituted furans from readily available acyclic precursors utilizing, in most cases, catalytic $CrCl_2$. Extensions of this methodology to the preparation of di- and trisubstituted furans are under active investigation, and the results will be the subject of future publications.

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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.asc.org.

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