Gold catalysed synthesis of 3-alkoxyfurans at room temperature†

 Matthew N. Pennell,^a Robert W. Foster,^a Peter G. Turner,^b Helen C. Hailes,^a
Christopher J. Tame^b and Tom D. Sheppard^{*a}

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Synthetically important 3-alkoxyfurans can be prepared efficiently via treatment of acetal-containing propargylic alcohols (obtained from the addition of 3,3-diethoxypropyne to aldehydes) with 2 mol% gold catalyst in an alcohol solvent at room temperature. The resulting furans show useful reactivity in a variety of subsequent transformations.

Furans are important structural motifs which appear in a wide array of natural products, biologically active compounds and pharmaceuticals.¹ They also have potential uses in the construction of conjugated polymers for applications such as organic electronics.² As a consequence, the synthesis of polysubstituted furans has attracted considerable interest. Recent synthetic approaches have included a number of transition-metal catalysed cyclisation reactions³ mediated by a variety of catalysts^{4–8} including systems based on palladium,⁴ rhodium,⁵ ruthenium⁶ and silver.⁷ Over the past few years, the use of homogeneous gold catalysts for facilitating the addition of nucleophiles to carbon–carbon multiple bonds has emerged as a very powerful synthetic method⁹ and a number of gold-catalysed approaches to the synthesis of heterocyclic aromatic rings,¹⁰ including simple furans,¹¹ have been reported. Simple 3-alkoxyfurans such as 3-methoxyfuran are highly electron rich systems which show useful reactivity,¹² and have found application in natural product synthesis¹³ as well as in the construction of polysubstituted tetrahydrofurans.¹⁴ However, the chemistry of more complex 3-alkoxyfurans has not been widely explored, largely as a consequence of their synthetic inaccessibility.¹⁵ Herein, we describe a gold-catalysed method for the synthesis of a wide variety of 3-alkoxyfurans from readily available propargylic alcohols, *via* a process that allows straightforward variation of substituents both on the furan ring and the alkoxy group.

We have recently reported that the gold-catalysed rearrangement of propargylic alcohols to enones (the Meyer–Schuster rearrangement) proceeds at room temperature in toluene, in the presence of a small amount of alcohol additive (MeOH or EtOH).¹⁶ During the course of our study into the scope of this reaction, we observed that attempted rearrangement of acetal-containing propargylic alcohol **1a** (Scheme 1, R¹ = 4-CF₃C₆H₄)

Scheme 1 Gold-catalysed synthesis of 3-ethoxyfurans and 3-methoxyfurans. ^a 600 mg scale reaction. ^b Clean conversion of the aldehyde in propargylic alcohol **1o** into the dimethylacetal occurred under the reaction conditions.

^a Department of Chemistry, University College London, 20 Gordon St, London, WC1H 0AJ, UK. E-mail: tom.sheppard@ucl.ac.uk; Fax: +44 (0)7679 7463; Tel: +44 (0)7679 2467

^b GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK

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gave a mixture of the expected enone **2a** and 3-ethoxyfuran **3a**, where the alcohol additive had become incorporated.¹⁷ Given the importance of polysubstituted furans in a wide variety of applications, we sought to optimise this transformation.¹⁸ Pleasingly in ethanol furan **3a** was formed in 89% yield with complete selectivity. With these optimised conditions in hand, the synthesis of a wide range of 3-ethoxyfurans and 3-methoxyfurans was then explored. High yields (68–98%) of the corresponding furans **3** and **4** were obtained with a selection of propargylic alcohols **1a–1o**. A wide range of aromatic groups can be incorporated at the 2-position of the furan ring, including electron deficient (**1a**, **1h**, **1m**), electron rich (**1c**, **1n**) and sterically encumbered (**1f**) benzene rings, as well as thiophene (**1i**) and furan (**1j**) rings. Propargylic alcohols containing aliphatic groups were also smoothly converted into the corresponding 2-alkyl furans (**1b**, **1d**, **1g**, **1k**). When methanol was used as the reaction solvent, direct solvolysis to generate the 3-methoxyfurans **4** occurred selectively over formation of 3-ethoxyfurans **3**, which could potentially occur *via* incorporation of an ethoxy group derived from the acetal group. Many functional groups including an alkene (**1g**), a nitrile (**1h**), a halide (**1l**), an ester (**1m**), and even a free phenol (**1n**) were compatible with the reaction. In the case of the aldehyde containing substrate **1o**, concomitant formation of the corresponding dimethylacetal **4o** was observed. The synthesis of furan **3b** was performed on a 600 mg scale without difficulty to give the alkyl furan in 85% yield.

The synthesis of more complex 3-alkoxyfurans was then explored, by incorporation of other alcohols in the furan formation reaction (Scheme 2). Primary (**5b**, **6b**, **7b**), secondary (**8b**) and tertiary (**9b**) alcohols were incorporated efficiently, including functionalised examples such as allyl alcohol (**6b**) and ethylene glycol (**7b**).

It was also possible to construct a conjugated bis-(3-alkoxy-2-furyl)benzene **4p** in excellent yield by gold-catalysed reaction of bis-propargylic alcohol **1p** with MeOH (Scheme 3). The conjugated triaryl unit in **4p** is reminiscent of the oligofuran systems currently being investigated for a variety of applications in organic electronics.² Interestingly, propargylic alcohol **1q** containing a nearby alkene unit underwent tandem alcohol addition/ene-yne cyclisation to give fused cyclohexylfurans **10** in excellent yield, with incorporation of the alcohol on the cyclohexane ring. This provides a rapid assembly of the fused furan-cyclohexane motif present in the terpene natural product furadysin.¹⁹

Appropriate control experiments¹⁸ were performed to demonstrate that the gold catalyst was required for the furan

Scheme 2 Incorporation of different alcohols in the 3-alkoxyfuran formation reaction with **1b**.

Scheme 3 Synthesis of polycyclic furans.

Scheme 4 Possible mechanism for the gold-catalysed conversion of propargylic alcohols **1** to furans **3**.

formation, and that the reaction was unlikely to be catalysed by Brønsted acid (Tf_2NH)²⁰ or silver salts (AgNTf_2).^{16b,21} The furan formation reaction potentially proceeds *via* regioselective gold-catalysed addition of the alcohol to the alkyne to generate vinyl gold intermediate **11** (Scheme 4). Loss of ethanol can then lead to allenyl ether **12** which can undergo further activation by gold to give oxonium ion **13**. Oxonium ion **13** can then be attacked by the nearby alcohol to generate dihydrofuran intermediate **14** which will evolve to the furan **3** after protodeauration and loss of ethanol. An alternative pathway which proceeds *via* Lewis-acid activation of the acetal to generate oxonium ion **15**, followed by conjugate addition of the alcohol to give **12**, can also be envisaged. However, this seems less likely given the fact that the furan formation does not readily occur in the presence of a simple Brønsted acid catalyst.¹⁸

The electron-rich 3-alkoxyfurans are highly reactive, and care should be taken during the isolation of these compounds in order to prevent decomposition of the products *via* atmospheric oxidation.¹⁸ The reactivity of these furan systems can nevertheless be readily harnessed in a variety of other useful transformations (Scheme 5). Furan **4b** readily underwent a Diels–Alder reaction with *N*-methylmaleimide at room temperature to generate the cycloadduct **16** as a 2:1 mixture of separable stereoisomers in excellent overall yield (94%). Treatment of the major diastereoisomer with TFA led to stereoselective cyclisation to give the polycyclic ether **17** in 69% yield. Cyclohexyl fused furan **10b** gave tertiary amine **18** in 92% yield upon reaction with Eschenmoser's salt.^{12a} We were also able to promote Claisen rearrangement²² of the allyloxyfuran **6b** by heating at reflux in toluene to generate 2,2-disubstituted 3-furanone **19** in 80% yield. Electrophilic bromination²³ of furan **3e** proceeded in 75% yield

Scheme 5 Selected reactions of the furan products.

to give bromide **20**, providing a useful building block for cross-coupling reactions.

In summary, we have developed a mild gold-catalysed method for the formation of synthetically useful 3-alkoxyfurans which enables these versatile molecules to be prepared in two steps from readily available aldehydes, alcohols and 3,3-diethoxypropyne. The reaction gives access to a wide range of 3-alkoxyfurans in good to excellent yield, and the products can be used in subsequent transformations to access more complex structures.

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