Gold catalysed synthesis of 3-alkoxyfurans at room temperature†

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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. They also have potential uses in the construction of conjugated polymers for applications such as organic electronics. As a consequence, the synthesis of polysubstituted furans has attracted considerable interest. Recent synthetic approaches have included a number of transition-metal catalysed cyclisation reactions mediated by a variety of catalysts including systems based on palladium, rhodium, ruthenium and silver. 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 method and a number of gold-catalysed approaches to the synthesis of heterocyclic aromatic rings, including simple furans, have been reported. Simple 3-alkoxyfurans such as 3-methoxyfuran are highly electron rich systems which show useful reactivity, and have found application in natural product synthesis as well as in the construction of polysubstituted tetrahydrofurans. However, the chemistry of more complex 3-alkoxyfurans has not been widely explored, largely as a consequence of their synthetic inaccessibility. 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). 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, \( R^3 = 4\text{-CF}_3\text{C}_6\text{H}_4 \))

Scheme 1  Gold-catalysed synthesis of 3-ethoxyfurans and 3-methoxyfurans.

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for all compounds and \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra for novel compounds. See DOI: 10.1039/c3cc48290a
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, 1b, 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 (1i), 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 experiments\(^{18}\) were performed to demonstrate that the gold catalyst was required for the furan formation, and that the reaction was unlikely to be catalysed by Brønsted acid (Tf₂NH)\(^{20}\) or silver salts (AgNTf₂)\(^{16,21}\). 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). Furans 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.\(^{15e}\) We were also able to promote Claisen rearrangement\(^{22}\) of the alkoxyfurans 6b by heating at reflux in toluene to generate 2,2-disubstituted 3-furanone 19 in 80% yield. Electrophilic bromination\(^{23}\) of furan 3e proceeded in 75% yield.
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 yield from readily available aldehydes, alcohols and 3,3-diethoxypropyne, which enables these versatile molecules to be prepared in two steps to access more complex structures.

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Notes and references

11 See ESII for further details.