

Gold catalysed synthesis of 3-alkoxyfurans at room temperature†

Cite this: DOI: 10.1039/c3cc48290a

Received 29th October 2013,
Accepted 11th December 2013

DOI: 10.1039/c3cc48290a

www.rsc.org/chemcomm

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.

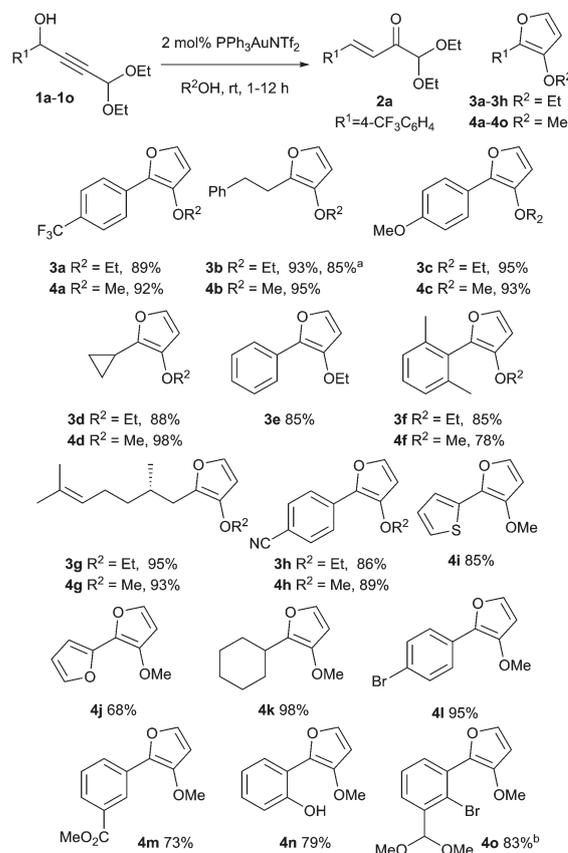
^a Department of Chemistry, University College London, 20 Gordon St, London, WC1H 0AJ, UK. E-mail: tom.sheppard@ucl.ac.uk; Fax: +44 (0)7679 7463; Tel: +44 (0)7679 2467

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

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for all compounds and ¹H and ¹³C NMR spectra for novel compounds. See DOI: 10.1039/c3cc48290a

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

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) gave a mixture of

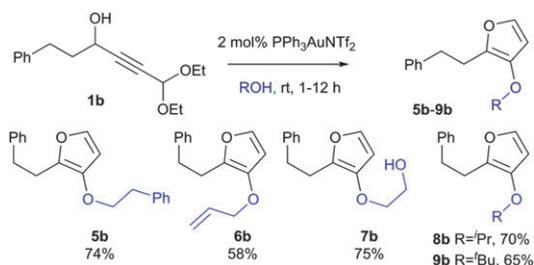


Scheme 1 Gold-catalysed synthesis of 3-ethoxyfurans and 3-methoxyfurans. ^a 600 mg scale reaction. ^b Clean conversion of the aldehyde in propargylic alcohol **1o** into the dimethylacetal occurred under the reaction conditions.

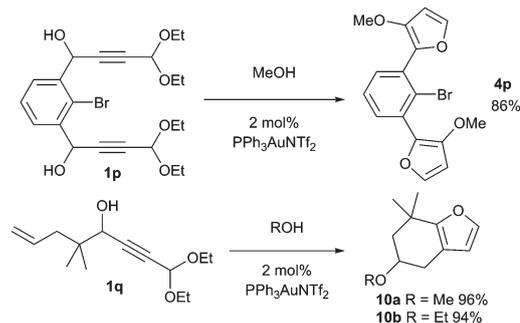
1 the expected enone **2a** and 3-ethoxyfuran **3a**, where the alcohol
 additive had become incorporated.¹⁷ Given the importance of
 polysubstituted furans in a wide variety of applications, we
 sought to optimise this transformation.¹⁸ Pleasingly in ethanol
 5 furan **3a** was formed in 89% yield with 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
 10 **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
 15 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
 20 derived from the acetal group. Many functional groups includ-
 ing 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
 25 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
 30 (**8b**) and tertiary (**9b**) alcohols were incorporated efficiently,
 including functionalised examples such as allyl alcohol (**6b**)
 and ethylene glycol (**7b**).

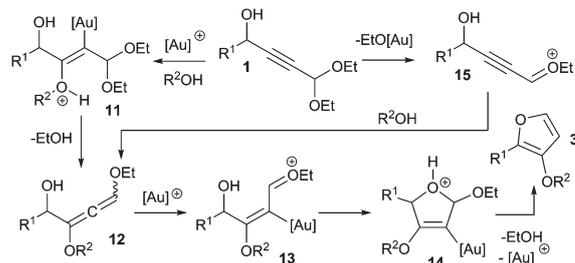
It was also possible to construct a conjugated bis-(3-alkoxy-2-
 furyl)benzene **4p** in excellent yield by gold-catalysed reaction of
 bis-propargylic alcohol **1p** with MeOH (Scheme 3). The con-
 35 jugated triaryl unit in **4p** is reminiscent of the oligofuran
 systems currently being investigated for a variety of applica-
 tions in organic electronics.² Interestingly, propargylic alcohol
1q containing a nearby alkene unit underwent tandem alcohol
 addition/ene-yne cyclisation¹⁹ to give fused cyclohexylfurans **10**
 40 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



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



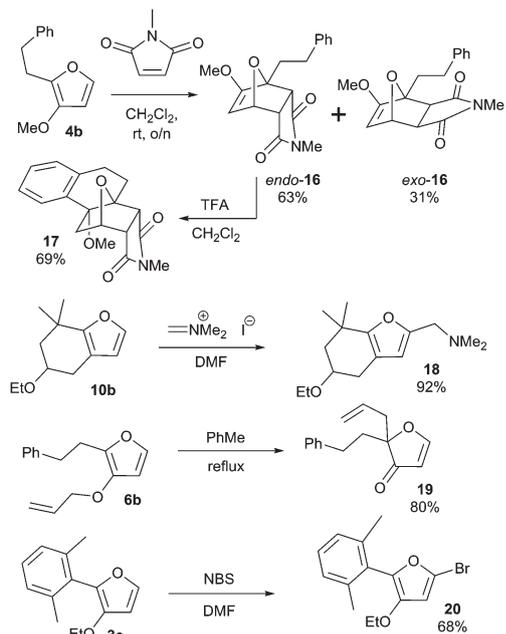
Scheme 3 Synthesis of polycyclic furans.



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

Appropriate control experiments¹⁸ 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 (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**
 35 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* atmo-
 spheric 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 tempera-
 45 ture to generate the cycloadduct **16** as a 2 : 1 mixture of separa-
 ble 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. Cyclo-
 hexyl fused furan **10b** gave tertiary amine **18** in 92% yield upon
 50 reaction with Eschenmoser's salt.^{12a} We were also able to
 promote Claisen rearrangement²² of the allyloxyfuran **6b** by



Scheme 5 Selected reactions of the furan products.

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 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.

We would like to acknowledge the Engineering and Physical Sciences Research Council (EP/E052789/1 and EP/G040680/1) and GlaxoSmithKline (CASE award, PhD studentship support and supply of selected aldehydes) for supporting this work.

Notes and references

- H. N. C. Wong, P. Yu and C.-Y. Yick, *Pure Appl. Chem.*, 1999, **71**, 1041.
- (a) O. Gidron, Y. Diskin-Posner and M. Bendikov, *J. Am. Chem. Soc.*, 2010, **132**, 2148; (b) A. T. Yiu, P. M. Beaujuge, O. P. Lee, C. H. Woo, M. F. Toney and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2012, **134**, 2180; (c) O. Gidron, A. Dadvand, Y. Sheynin, M. Bendikov and D. F. Perepichka, *Chem. Commun.*, 2011, **47**, 1976; (d) U. H. F. Bunz, *Angew. Chem., Int. Ed.*, 2010, **49**, 5037; (e) T. Fallon, A. C. Willis, A. D. Rae, M. N. Paddon-Row and M. S. Sherburn, *Chem. Sci.*, 2012, **3**, 2133.
- (a) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084; (b) W. J. Moran and A. Rodriguez, *Org. Prep. Proced. Int.*, 2012, **44**, 103.
- (a) M. Zheng, L. Huang, W. Wu and H. Jiang, *Org. Lett.*, 2013, **15**, 1838; (b) C. Song, L. Ju, M. Wang, P. Liu, Y. Zhang, J. Wang and Z. Xu, *Chem.-Eur. J.*, 2013, **19**, 3584.
- (a) P. Lenden, D. A. Entwistle and M. C. Willis, *Angew. Chem., Int. Ed.*, 2011, **50**, 10657; (b) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2013, **52**, 629.

- (a) B. Schmidt and D. Geißler, *Eur. J. Org. Chem.*, 2011, 7140; (b) B. Schmidt and D. Geißler, *Eur. J. Org. Chem.*, 2011, 4814; (c) K. Yamashita, Y. Yamamoto and H. Nishiyama, *J. Am. Chem. Soc.*, 2012, **134**, 7660.
- C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen and A. Lei, *J. Am. Chem. Soc.*, 2012, **134**, 5766.
- (a) X. Cui, X. Xu, L. Wojtas, M. M. Kim and X. P. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 19981; (b) H. Jiang, W. Zeng, Y. Li, W. Wu, L. Huang and W. Fu, *J. Org. Chem.*, 2012, **77**, 5179; (c) C. Wang, Z. Li, Y. Ju and S. Koo, *Eur. J. Org. Chem.*, 2011, 6976; (d) V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 8486; (e) H. Cao, H. Zhan, J. Wu, H. Zhong, Y. Lin and H. Zhang, *Eur. J. Org. Chem.*, 2012, 2138; (f) A. W. Sromek, A. V. Kel'in and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2004, **43**, 2280.
- Modern Gold Catalyzed Synthesis*, ed. A. S. K. Hashmi and F. D. Toste, Wiley-VCH, Weinheim, 2012.
- (a) P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931; (b) C. Gronnier, Y. Odabachian and F. Gagosz, *Chem. Commun.*, 2011, **47**, 218; (c) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; (d) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, *Org. Lett.*, 2010, **12**, 2594; (e) S. Ngwerume and J. E. Camp, *Chem. Commun.*, 2011, **47**, 1857; (f) Z.-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624.
- (a) Y. Li, K. A. Wheeler and R. Dembinskia, *Adv. Synth. Catal.*, 2010, **352**, 2761; (b) H. Gao, X. Wu and J. Zhang, *Chem.-Eur. J.*, 2011, **17**, 2838; (c) X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 8886; (d) F. Liu, D. Qian, L. Li, X. Zhao and J. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6669; (e) A. S. K. Hashmi, T. Häffner, M. Rudolph and F. Rominger, *Eur. J. Org. Chem.*, 2011, 667; (f) E. Li, W. Yao, X. Xie, C. Wang, Y. Shao and Y. Li, *Org. Biomol. Chem.*, 2012, **10**, 2960; (g) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 7200; (h) E. Wang, X. Fu, X. Xie, J. Chen, H. Gao and Y. Liu, *Tetrahedron Lett.*, 2011, **52**, 1968; (i) P. Nun, S. Dupuy, S. Gaillard, A. Poater, L. Cavallo and S. P. Nolan, *Catal. Sci. Technol.*, 2011, **1**, 58; (j) J. Li, L. Liu, D. Ding, J. Sun, Y. Ji and J. Dong, *Org. Lett.*, 2013, **15**, 2884.
- (a) C. Meister and H. D. Scharf, *Synthesis*, 1981, 737; (b) A. Murai, K. Takahashi, H. Taketsuru and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1981, 221.
- (a) J. D. Brubaker and A. G. Myers, *Org. Lett.*, 2007, **9**, 3523; (b) J. H. Frederich and P. G. Harran, *J. Am. Chem. Soc.*, 2013, **135**, 3788; (c) K.-I. Takao, H. Ochiai, K.-I. Yoshida, T. Hashizuka, H. Koshimura, K.-I. Tadano and S. Ogawa, *J. Org. Chem.*, 1995, **60**, 8179; (d) K. Okada, M. Mizuno, H. Sasaki, K. Sugiura, H. Tanino, H. Kakoi and S. Inoue, *Heterocycles*, 1991, **32**, 431.
- T. J. Donohoe, A. A. Calabrese, J.-B. Guillermin, C. S. Frampton and D. Walter, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1748.
- (a) S. Nakatani, M. Kiriara, K. Yamada and S. Tereshima, *Tetrahedron Lett.*, 1995, **36**, 8461; (b) P. Truong, X. Xu and M. P. Doyle, *Tetrahedron Lett.*, 2011, **52**, 2093; (c) A. F. Thomas and H. Damm, *Tetrahedron Lett.*, 1986, **27**, 505; see also ref. 12–13.
- (a) M. N. Pennell, M. G. Unthank, P. Turner and T. D. Sheppard, *J. Org. Chem.*, 2011, **76**, 1479; (b) M. N. Pennell, P. G. Turner and T. D. Sheppard, *Chem.-Eur. J.*, 2012, **18**, 4748.
- D. Obrecht, *Helv. Chim. Acta*, 1989, **72**, 447.
- See ESI† for further details.
- R. Kazlauskas, P. T. Murphy, R. J. Wells, J. J. Daly and P. Schönholzer, *Tetrahedron Lett.*, 1978, **19**, 4951.
- (a) C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, *Chem-CatChem*, 2010, **2**, 1226; (b) P. Starkov, F. Rota, J. M. D'Oyley and T. D. Sheppard, *Adv. Synth. Catal.*, 2012, **354**, 3217; (c) A. S. K. Hashmi, L. Schwarz, P. Rubenbauer and M. C. Blanco, *Adv. Synth. Catal.*, 2006, **348**, 705; (d) A. S. K. Hashmi, *Catal. Today*, 2007, **122**, 211; (e) T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, **76**, 9353.
- (a) A. S. K. Hashmi, in *Silver in Organic Chemistry*, ed. M. Harmata, John Wiley and Sons, Hoboken, 2010, pp. 357–359; (b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012.
- R.-C. Gebel and P. Margaretha, *Helv. Chim. Acta*, 1992, **75**, 1633.
- M.-A. Raheem, J. R. Nagireddy, R. Durham and W. Tam, *Synth. Commun.*, 2010, **40**, 2138.