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Furan synthesis through $AuCl_3$-catalysed cycloisomerisation of β-alkynyl β-ketoesters

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ABSTRACT

$AuCl_3$ efficiently catalyses the cycloisomerisation of readily available β-alkynyl β-ketoesters to generate trisubstituted furans. The substrate scope is wide and the reaction is high yielding and operationally simple.

The furan ring is an important structural sub-unit present in many natural products[1] and drug molecules. Numerous synthetic furan derivatives have been shown to exhibit a wide range of biological activities.[2] Furans have also been incorporated into polymers and macrocycles for materials applications.[3] In addition, the utility of furans as building blocks in synthesis has received considerable attention.[4] Accordingly, the development of new and efficient syntheses of multi-substituted furan rings is an important objective.

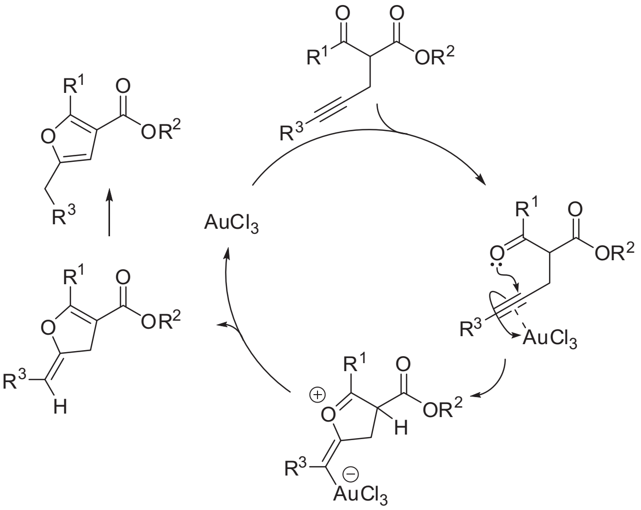
Cycloisomerisation reactions are powerful methods for the preparation of cyclic compounds because of their 100% atom economy. In particular, the recent explosion of interest in gold catalysis has revealed many such systems that generate a variety of ring structures.[5]

As part of our research programme, we became interested in electrophilic cyclisation reactions onto alkynes. Au-catalysed 5-*endo-dig* cycloisomerisations of alkynyl substrates to generate furan rings have been reported for a number of systems, namely: (*Z*)-alk-2-en-4-yn-1-ols,[6] alka-2,3-dien-1-ones,[7] alk-3-yn-1-ones[8] and alkynyloxiranes.[9] A variety of other metal-catalysed furan syntheses have also been reported.[10]

Herein we report our observation that β-alkynyl β-ketoesters undergo 5-*exo-dig* cycloisomerisation with a catalytic amount of gold(III) chloride in refluxing methanol to generate trisubstituted furan rings in good yields. $PtCl_2$ was also found to be an effective catalyst for this reaction, but slightly diminished yields were obtained.

Belting and Krause have reported a similar 5-*exo-dig* cycloisomerisation reaction of β-alkynyl ketones employing Au(I) catalysis.[11] Interestingly, with their substrates, $AuCl_3$ only produced trace amounts of the furan product, and the use of alcohol solvents with their Au(I) catalyst system led to the generation of tetrahydrofuranyl ethers instead of furans.

For our study, the substrates were readily prepared either by alkylation of the requisite dicarbonyl compounds with the corresponding substituted propargylic bromide or by alkylation with



Scheme 1. Postulated cycloisomerisation mechanism.

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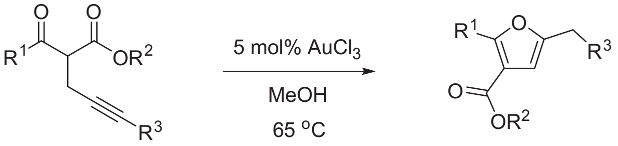
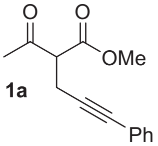
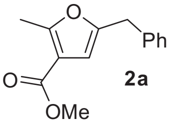
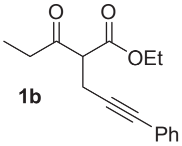
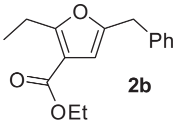
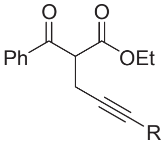
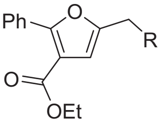
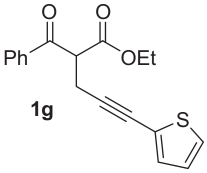
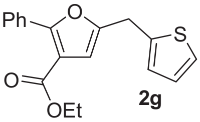
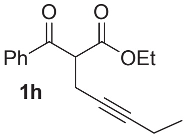
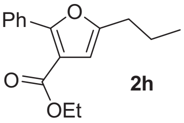
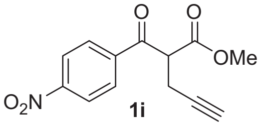
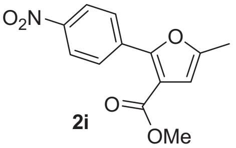
Table 1
$AuCl_3$-catalysed cycloisomerisation to furans



Entry	Alkyne	Product	Yield[a] (%)
1	 **1a**	 **2a**	73
2	 **1b**	 **2b**	71[b]
			
3	**1c** R = H	**2c**	77
4	**1d** R = Ph	**2d**	78
5	**1e** R = *p*-C_6H_4Cl	**2e**	68
6	**1f** R = *p*-C_6H_4OMe	**2f**	54
7	 **1g**	 **2g**	32
8	 **1h**	 **2h**	51
9	 **1i**	 **2i**	99[b]

[a] Yield of pure isolated product.
[b] Reaction run in dry methanol.

propargyl bromide followed by Sonogashira coupling. The subsequent cycloisomerisation was found to be effective for all of the substrates tested (Table 1).

Alkyne **1a** cycloisomerised to furnish the furan **2a** in very good yield in refluxing methanol. However, alkyne **1b** underwent competitive alkyne hydration under these conditions,[12] therefore, dry methanol was required in order to obtain **2b** in high yield. Alkyne **1c** containing a terminal alkyne cyclised efficiently under the reaction conditions. Cycloisomerisations of **1d**–**f** demonstrated a slight electronic effect with *p*-chlorophenyl and *p*-methoxyphenyl alkyne substituents giving slightly diminished yields of the furan compared to the phenyl (entries 4–6). The reaction was also successful with a thiophene alkyne substituent generating bis(heteroaryl)methane **2g**, but in low yield (entry 7). An alkyl substituted alkyne proved to be a good substrate for this reaction (entry 8). Intriguingly, *p*-nitrophenylketone alkyne **1i**, underwent quantitative cycloisomerisation, however, dry methanol was required to minimise alkyne hydration in this case as well (entry 9).

The cycloisomerisation is proposed to proceed through alkyne activation by Au(III) and subsequent intramolecular attack by the ketone oxygen to form a zwitterionic intermediate. Protodemetalation regenerates the gold catalyst and releases the heterocycle, which isomerises to the furan product (Scheme 1).[13]

In conclusion, an operationally simple procedure for the preparation of functionalised furans from readily available β-alkynyl β-ketoesters through gold catalysis is reported.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, characterisation data and ^{1}H and ^{13}C NMR spectra for all novel compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.086.

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