

An efficient furan synthesis using heterogeneous catalysis

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Received 20 July 2007; accepted 6 August 2007

Available online 1 September 2007

Abstract—A wide variety of 3-alkyne-1,2-diols have been found to undergo exceptionally clean 5-*endo*-dig cyclisations followed by dehydration at ambient temperature to give the corresponding furans in essentially quantitative yields when exposed to 10 mol % of 10% w/w silver(I) nitrate absorbed on silica gel.

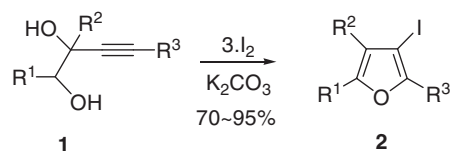
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Despite the best efforts of synthetic chemists during more than a century of research, there still remains a need to define new methods for the elaboration of heteroaromatics which have the degree of flexibility and generality demanded by modern compound discovery programmes. This is significantly exacerbated by the ever-increasing demands for environmental protection and hence the use of a clean technology. The importance of such compounds to the pharmaceutical sector alone is self-evident from the statistic that some 70% of drug therapies in use today contain at least one such residue. If this were not enough, heteroaromatics play key roles in many other groups of ‘effect’ chemicals, ranging from plastics, conducting polymers, agrochemicals, flavours and fragrances and photochromic and other new materials to name but a few.¹

There are arguably two basic strategies for synthesis in this area: prepare a suitable acyclic precursor and cyclise this to give the heteroaromatic target or elaborate a simpler parent heteroaromatic using appropriate combinations of electrophilic and sometimes nucleophilic reagents. A potentially attractive version of these methods, which can be regarded as a combination of both strategies, is to carry out the cyclisation of an acyclic precursor using a triggering reagent which remains in the final product and which can subsequently be used for further homologations. An example of this is our use of 5-*endo*-dig iodocyclisations to convert 3-alkyne-1,2-diols **1** into the corresponding β-iodofurans **2**

(Scheme 1).² Clearly, the residual iodine atom used to induce the cyclisation can subsequently be deployed to introduce additional groups, especially by using one of the plethora of palladium-catalysed coupling methods which are now available,³ as well as the methods based around halogen–lithium exchange.⁴

At the time of our first report of this iodocyclisation, the 5-*endo*-dig cyclisation mode was something of a ‘Cinderella’ reaction, despite being favoured according to Baldwin’s rules⁵ and some earlier indications of its viability using mercury(II) salts to induce cyclisations related to those shown in Scheme 1.⁶ There have subsequently been a number of reports of alternative approaches to furans,⁷ which feature 5-*endo* cyclisations.⁸ These include halide-induced cyclisations of 1,4-diaryl-but-3-yn-1-ones⁹ and cyclisations wherein Michael additions of a nucleophile, usually a simple alcohol, complete formation of furans from conjugated enones following exposure to a triggering electrophile,¹⁰ including iodonium species and also gold(III)¹⁰ and copper(I) salts.¹¹ Conjugated ynones have also been transformed into furans upon exposure to copper(I) salts in a sequence, which strongly suggests the intermediacy of the corresponding allenes,¹² not surprisingly, Hashmi’s group



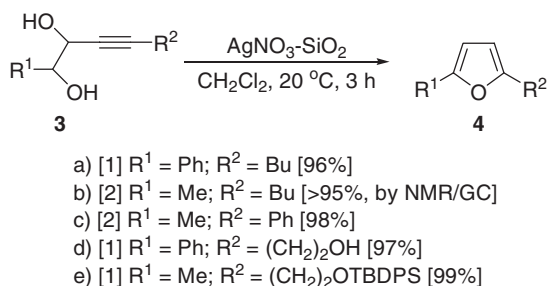
Scheme 1.

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have shown that both these types of precursors are useful as furan precursors, especially when using gold(III) salts.¹³ Allenic intermediates are also often featured in the base-catalysed cyclisations of similar precursors developed by Marshall and DuBay.¹⁴ Silver(I) salts have also long been known to be capable of activating allenes in cyclisation reactions. For example, both alcohol and acid groups can be thus induced to undergo 5-*endo* cyclisations to give 2,5-dihydrofurans¹⁵ or butenolides,¹⁶ respectively. Conjugated allenic ketones and suitable alkynyl-pyrimidinones are both converted into the corresponding furans using silver(I) nitrate,¹⁷ following the lead provided by the Marshall group, who found that 2-alkynyl-allylic alcohols could be converted into the corresponding furans very efficiently using silver(I) nitrate on silica gel.¹⁸

It was against this background that we began to investigate the prospects for achieving the conversion of 3-alkyne-1,2-diols **1** (see Scheme 1) into furans using metal catalysts.⁶ Our ultimate aim was to define a heterogeneous catalyst, which could be recycled and which would offer all of the advantages usually associated with such reagents, in contrast to the related homogeneous catalysts such as gold(III) salts. Although spectacularly successful in triggering 5-*endo*-dig and other cyclisations, their removal might give rise to problems, especially on scale-up.¹³ In the event, we were delighted to find that 10% w/w silver(I) nitrate on silica gel, a material more often associated with the chromatographic separation of alkene stereoisomers, was especially effective. The initial results leading to 2,5-disubstituted furans **4** are shown in Scheme 2. The numbers in square brackets ([1]; [2]) refer to the method of precursor synthesis, as explained below. The yields are the averages of a number of runs in each case.

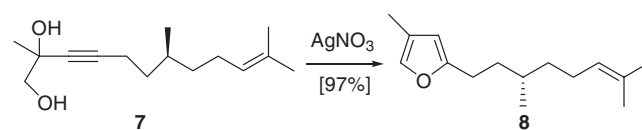
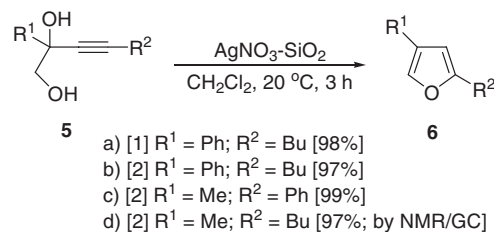
However, as far as it could be judged, these conversions were quantitative and the slight losses were simply mechanical or due to product volatility; we could not detect any by-product formation. Although we carried out all of these cyclisations in dry dichloromethane, hexane worked equally well and in some cases, cyclisations were faster in this solvent.¹⁸ The rate of cyclisation could also be enhanced both by heating and by passage through a column of catalyst contained in a microwave oven.¹⁹ However, while this was not at the expense of by-product formation, it was judged not worthwhile to modify an already quantitative conversion in these



Scheme 2.

ways, as yields were essentially perfect after simply stirring the catalyst with the precursor for 3 h at ambient temperature.

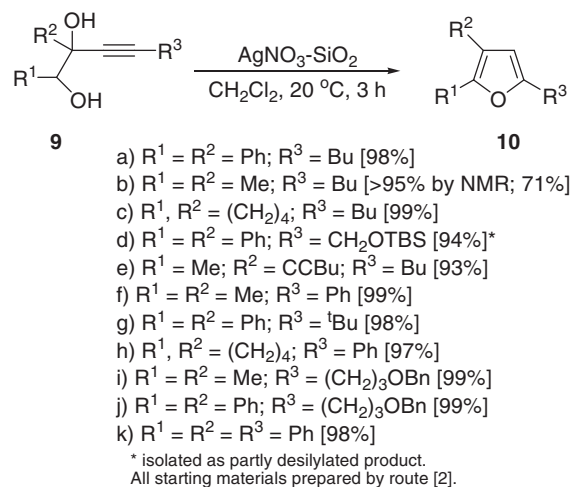
Much the same pattern of essentially quantitative conversions was observed in syntheses of representative 2,4-disubstituted furans **6** from the corresponding 3-alkyne-1,2-diols **5** (Scheme 3).



Scheme 3.

Due to its volatility, furan **6d** was assayed by a combination of NMR and GC analysis. An indication of the mildness of the procedure is given by the completely clean conversion of the citronellol-derived diol **7** into the sesquirosefuran isomer **8** in essentially quantitative yield. These results are particularly pleasing as the 2,4-disubstitution pattern is quite difficult to obtain. Our method featuring 2-lithio-4-methylfuran²⁰ is one of the few available for the elaboration of terpenoid targets in this area.²¹

A final series featured the synthesis of 2,3,5-trisubstituted furans **10** from the corresponding alkyne-diols **9** (Scheme 4). Again, all yields were essentially quantitative, no matter if the substituents were alkyl or aryl groups or large *t*-butyl groups (**10g**). The only slight



Scheme 4.

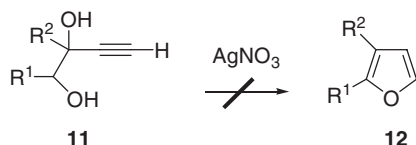
complication was the partial loss of the *t*-butyldimethylsilyl (TBS) protecting group during cyclisation of the propargyl alcohol derivative **9d**. However, the combined yield, after chromatographic separation of the *O*-silyl derivative and the corresponding free alcohol, was still 94%. There was no interference from competing 5-*exo*-dig cyclisations involving the distal *O*-benzyl functions in reactions of the pentynol derivatives **9i,j** (Scheme 4).

Some limitations:- Inevitably, some limitations to these otherwise extremely efficient cyclisations came to light.

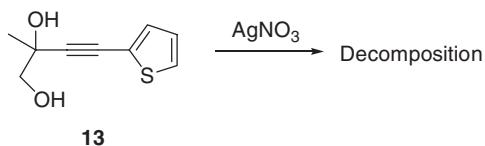
The most serious was the complete failure of 1-alkyne-3,4-diols **11** to undergo cyclisation to give examples of the 2,3-disubstitution pattern **12** (Scheme 5). The corresponding trimethylsilylated alkynes underwent protodesilylation. Efforts to overcome this limitation are in progress.

The method also appears to be incompatible with the presence of divalent sulfur: exposure of the 2-thienyl derivative **13** to silver nitrate on silica gel caused complete decomposition (Scheme 6). Therefore, thioether functions in general would also probably not survive; it seems unlikely that anything can be done to address this limitation.

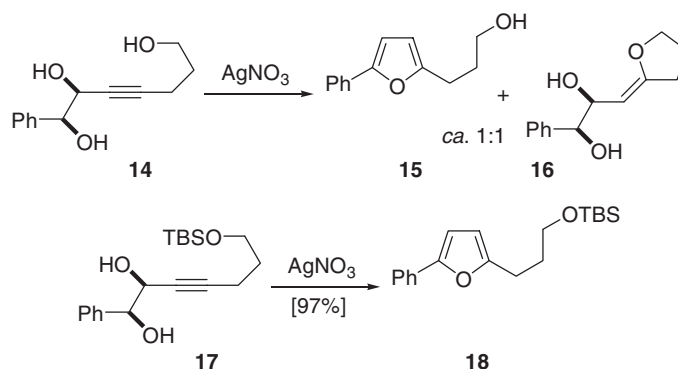
Finally, 5-*exo*-dig cyclisations can compete with the desired 5-*endo*-dig processes (Scheme 7). For example, expo-



Scheme 5.



Scheme 6.



Scheme 7.

sure of triol **14** to $\text{AgNO}_3\text{-SiO}_2$ under the usual conditions (see below) led to a ca. 1:1 mixture of the expected furan **15** together with ylidene-tetrahydrofuran **16**. Fortunately, this event could be blocked by masking the primary hydroxyl as its TBS ether **17**, in which case only the furan product **18** was obtained,²² in a similar fashion to the smooth reactions of the *O*-benzyl derivatives **9i,j** (Scheme 4). This bodes well, as silyl groups can easily be lost in related cyclisations of this type.²²

Starting material synthesis:- There are clearly a variety of approaches to the precursor 3-alkyne-1,2-diols **3**, **5**, **7** and **9**. During this study, two approaches were used: route [1] (Scheme 2) comprised a Sonogashira coupling²³ between the corresponding 1-haloalkene and 1-alkyne followed by regioselective bis-hydroxylation of the resulting conjugated enyne,²⁴ as previously employed by us.² Route [2] (Schemes 2–6) comprised condensations between α -silyloxy-aldehydes or ketones and lithio- or magnesio-acetylides (tetrahydrofuran, 0 °C). To obviate the need for a deprotection step, when the 1-alkyne was volatile (e.g., 1-hexyne) and hence easily removed from the products, 2.2 equiv of the lithio-acetylide was reacted directly with the hydroxy-carbonyl compound. In all cases, overall yields were in excess of 80% for one or two steps.

The actual cyclisations were carried out by stirring a solution of the 3-alkyne-1,2-diol in dichloromethane with 10 mol % of commercial 10% w/w silver(I) nitrate on silica gel at ambient temperature for around 3 h (TLC monitoring), followed by filtration through a silica gel pad eluted with dichloromethane. The only precaution was to exclude light from the reaction mixture by wrapping the flask in aluminium foil. Filtration through silica gel rather than using other methods was necessary to remove the small amount of silver salt, which was found to leach from the catalyst. If this slight weight loss was taken into account, the catalyst isolated by paper filtration retained essentially the same reactivity for at least two subsequent runs with the same or other 3-alkyne-1,2-diols.

This highly efficient furan synthesis would seem to have the potential to contribute an environmentally friendly method to the synthetic armoury in this and perhaps other areas of heterocyclic synthesis. Efforts to illustrate

these aspects are underway, as are modifications aimed at obviating the drawback of the slight silver leaching during the final filtration.²⁵

Acknowledgements

We are very grateful to the EPSRC Mass Spectrometry Service, University College Swansea, for the provision of high resolution mass spectrometric data and to GSK and the EPSRC for financial support.

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