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# Practical alternatives for the synthesis of β-iodofurans by 5-*endo*-dig cyclisations of 3-alkyne-1,2-diols

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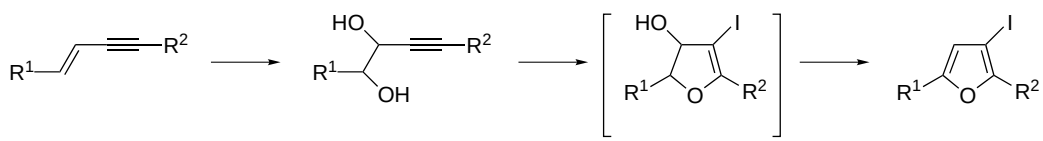
**Abstract**—Iodocyclisations of 3-alkyne-1,2-diols, obtained from acetylides and α-hydroxy-ketones or esters, give generally excellent yields of β-iodofurans by 5-*endo*-dig cyclisation followed by dehydration. 

Halogenated heteroaromatics have always occupied an important position as highly valuable intermediates in general organic synthesis, a status much enhanced by recent developments in radical chemistry and especially in transition metal-catalysed coupling reactions.[1] In general, the reactivity of five-membered heteroaromatics dictates that α-halo derivatives are usually readily available whilst the preparation of β-halo isomers has to rely on suitably powerful directing effects from existing α-substituents if viable levels of regioselection are to be achieved.[2] Further, in many cases, subsequent removal of such directing or blocking groups is necessary to provide a desired target by, for example, decarboxylation of an α-carboxylic acid function. For some time, we have been investigating the characteristics of electrophile-driven 5-*endo*-trig cyclisations which turn out to be extremely useful for the stereoselective elaboration of highly substituted tetrahydrofurans and pyrrolidines.[3] We wondered whether such cyclisation methodology could be extended to the related 5-*endo*-dig mode which, in contrast to 5-*endo*-trig processes, is favoured according to Baldwin's rules.[4] Despite this, such *endo*-dig cyclisations have been much less exploited in general, as has been highlighted recently by Carreira,[5] even though there are a number of hints in the older literature which indicate that these could have considerable synthetic potential.[6] More recent examples generally feature palladium-catalysed cyclisations, exemplified by a useful approach to indoles from 2-alkynylaniline derivatives.[1,7]

It was against this background that we developed the new approach to β-iodofurans summarised in Scheme 1.[8] The key step is an iodine-induced 5-*endo*-dig cyclisation of the acetylenic diols **2**, readily prepared by highly regioselective bis-hydroxylations of the corresponding enynes **1**.[9] Dehydration of the presumed intermediate hydroxy-dihydrofurans **3** was evidently very rapid, as these were not observed; only good to excellent yields of the iodofurans **4** were isolated. In general, β-iodofurans are not easy to prepare selectively, especially when the two existing α-substituents are electronically similar. The success of this type of cyclisation, as well as of a variety of subsequent homologation reactions involving replacement of the iodine atom by carbon-based substituents,[8] led us to investigate alternative and potentially more practical approaches to intermediates **2** and the viability or otherwise of iodocyclisations of these new precursors. Herein, we report that condensations between acetylides and both α-hydroxy-ketones and α-hydroxy-esters satisfy these criteria.




**1** **2** **3** **4**

**Scheme 1.**

*Keywords*: iodocyclisation; 5-*endo*-dig; β-iodofurans; 3-alkyne-1,2-diols; furans.

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Our starting point was a concern that, during our initial study,[8] no examples involving the presence of a second β-substituent, and thus cyclisations of diols in which one hydroxyl was tertiary, had been evaluated (see Scheme 1). We chose to exemplify this using a methyl group, since the β-methylfuran substructure is a feature of many furanoterpenes. Condensation between the tetrahydropyranyl ether **5**[10] of hydroxyacetone and 1-hexynyl lithium followed by deprotection gave an excellent yield of the acetylenic diol **6a**. Subsequent exposure to 3 equivalents each of iodine and sodium hydrogen carbonate in acetonitrile at 0°C led to a 56% isolated yield of the hoped for iodofuran **7a** (Scheme 2). Similarly, by starting with phenylacetylene, the 2-phenyl analogue **7b** was obtained in 61% isolated yield. These returns were slightly lower than expected. Combined GC–MS analysis of the reaction mixtures suggested these were higher (ca. 80%) and also revealed slower formation of additional products, the diiodides **8**, which presumably arise by direct iodination of the initial iodofurans **7** at the vulnerable free α-position. A brief optimisation study showed that the cyclisations were faster in dichloromethane and were also viable in tetrahydrofuran. For ease of work up, we used the former, when cyclisation was complete after approximately 5 h at 0°C. After this, substantial quantities of the diiodides **8** were formed; the lower isolated yields are also probably a consequence of product volatility.

Clearly, when the remaining α-position in the final β-iodofurans is substituted, then further iodination is not a problem. To probe the viability of such substrates in this chemistry, we examined similar chemistry using commercial 3-hydroxy-2-butanone **9** and 2-hydroxycyclohexanone[10] as starting materials.

In the interests of atom efficiency and time, these were treated directly with solutions of lithio-alkynes (1.1 equiv.) containing an additional equivalent of butyllithium, to obviate the need to protect the free hydroxyl group. This resulted in isolation of the required diols **11** and **12** in 70–75% yields (Scheme 3). The key cyclisations were carried out in dichloromethane, again using 3 equivalents each of $I_2$ and $NaHCO_3$, mixed at 0°C followed by stirring without further cooling for 3 h. A simple work-up[3] then gave the β-iodofurans **13** and **14** in 88–93% isolated yields.

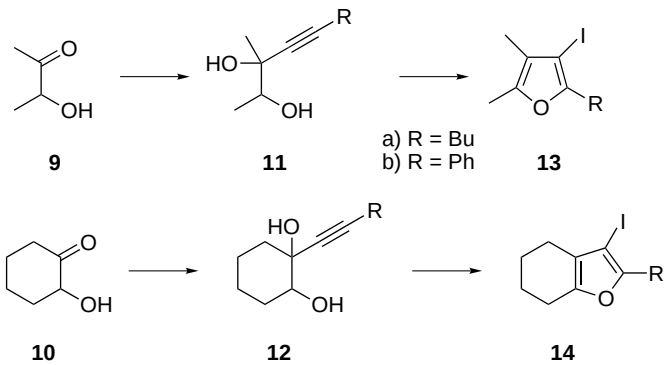
Other possibilities were also examined. Thus, the *O*-silyl derivative **15** of benzoin condensed smoothly with lithiated trimethylsilylacetylene to provide the alkyne-diol **16** following desilylation using fluoride; subsequent Sonogashira coupling[11] with 2-iodothiophene then gave the cyclisation precursor **17** (Scheme 4). Exposure to the usual iodocyclisation conditions in acetonitrile led to a 71% isolated yield of the fully substituted furan **18**.

Similarly, furoin **19** was converted into the alkyne-diol **20** (Scheme 5). Iodocyclisation failed in the usual solvents but delivered a 25% isolated yield of the trifurylfuran **21** if carried out in ethyl acetate, the poor return reflecting both product sensitivity and iodination of the vacant α-positions of the furyl residues.[12]

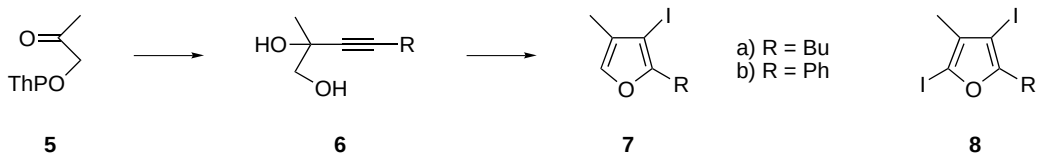
We then examined the prospects of using α-hydroxy-esters as starting materials, with a view to carrying a second alkyne function through the key cyclisation step. Thus, the bis-acetylenic diols **24** were prepared by condensations between the protected hydroxy-esters **22** and 2 equivalents of a lithio acetylide or between the parent hydroxy-esters **23** and 3 equivalents of acetylide (Scheme 6).

Overall yields for the former, two-step process were 62–83% while the latter direct condensation delivered 66–86% isolated yields of the diols **24**. As detailed in Scheme 6, these then underwent smooth cyclisations in acetonitrile to provide excellent yields of the acetylenic β-iodofurans **25**. The cyclisations were remarkably clean and could be carried out with equal facility on both the *O*-silyl precursors [**24**; $R^3 = SiBu^tMe_2$] or the free alcohols [**24**; $R^3 = H$] although, in the former case, it was essential that ca. 5% water was present. Both sets of substrates gave ca. 90% isolated yields of the iodofurans during 1 h or less at ambient temperature. By further homologations,[8] such compounds may find use in the elaboration of highly extended π-systems.

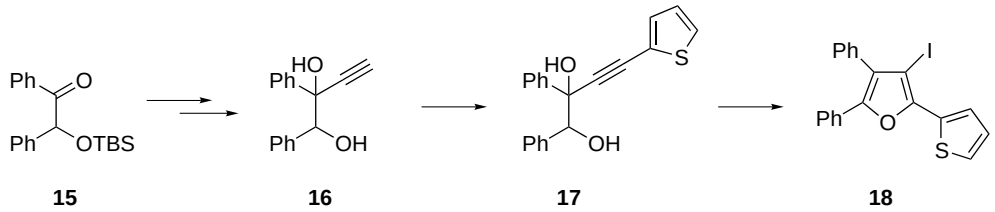
In summary, this modified approach to β-iodofurans offers flexibility, is usually very efficient and should be amenable to large scale synthesis. On the negative side, the availability of α-hydroxy-ketones or -esters could




**Scheme 3.**

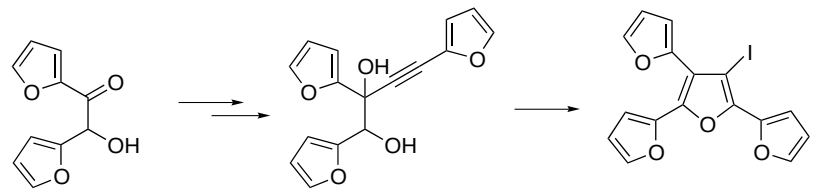



**Scheme 2.** *Reagents and conditions*: (i) RCCLi, −78°C, THF; (ii) 3 equiv. $I_2$ and $NaHCO_3$, $CH_2Cl_2$, 0°C.



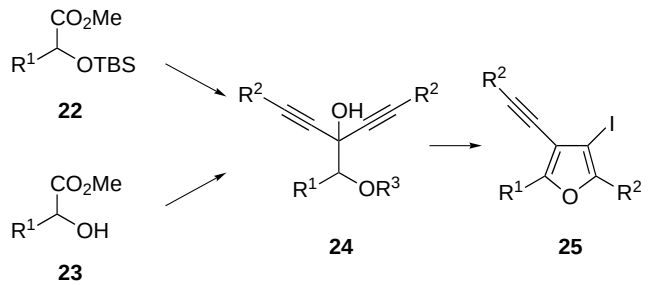

**15** **16** **17** **18**

**Scheme 4.**




**19** **20** **21**

**Scheme 5.**




**Yields of 25 from 24**

$R^1$ = Me; $R^2$ = Bu; $R^3$ = TBS [82%]
$R^1$ = Me; $R^2$ = Bu; $R^3$ = H [93%]
$R^1$ = Me; $R^2$ = Ph; $R^3$ = TBS [90%]
$R^1$ = Me; $R^2$ = Bu; $R^3$ = H [93%]
$R^1$ = Ph; $R^2$ = Bu; $R^3$ = H [87%]
$R^1$ = $R^2$ = Ph; $R^3$ = TBS [90%]
$R^1$ = $R^2$ = Ph; $R^3$ = H [94%]
$R^1$ = Me; $R^2$ = $CH_2OTBDPS$; $R^3$ = TBS [93%]

**Scheme 6.**

present a problem in some cases, although there is a plethora of methods available for the synthesis of these starting materials. The alkynylfurans **25** will always have an element of symmetry ($R^2$) as 2 equivalents of a single lithio-alkyne are used in their preparation; even if this were not the case, iodocyclisation of diol derivatives **24** having differing alkyne substituents may well not be regiospecific. Otherwise, this chemistry should make many types of highly substituted β-iodofurans very readily available.[13]

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12. Unfortunately, all subsequent attempts to couple this sensitive compound with various 2-furylmetals, under palladium catalysis, failed to deliver tetrafurylfuran.
13. Satisfactory spectroscopic and analytical data were obtained for all compounds reported herein.