Novel Ruthenium-catalysed Synthesis of Furan Derivatives *via* Intramolecular Cyclization of Hydroxy Enynes

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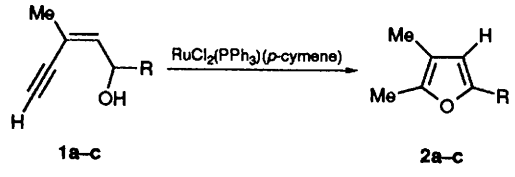
Furans containing a functional group at C(5) are obtained under neutral conditions by selective cyclization of (*Z*)-pent-2-en-4-yn-1-ols in the presence of $RuCl_2(PPh_3)$(*p*-cymene) as catalyst precursor.

Furan derivatives are useful natural compounds displaying interesting properties in flavour or fragrance, or for use in pharmaceutical chemistry.[1] They constitute an important class of synthetic intermediates for the access to a variety of heterocyclic and acyclic compounds.[2] Numerous synthetic approaches to furans are available and several methods already involve acetylenic derivatives. The intramolecular C–O bond formation from alkynols catalysed by strong bases like Bu^{t}OK has been reported starting from propynylic derivatives,[3] alcohols containing the conjugated enyne moiety[4,5] or alkynyl epoxides;[6] however, these strategies are not suitable for the synthesis of furans from base-sensitive substrates. Several selective transformations of acetylenic alcohols into furans under milder conditions using metal derivatives have been developed. They usually proceed *via* cyclization accompanied by rearrangement in the presence of mercury(II) salts,[7] dehydration,[8,9] or cleavage of a leaving group[8] with palladium catalysts. The formation of furans is also possible by cyclization of enolizable ketonic alkynes in the presence of palladium complexes.[10] We now report a novel ruthenium-catalysed synthesis of furans based on the intramolecular addition of an alcohol functionality to a terminal triple bond that tolerates functional groups sensitive to bases.

The reaction of 10 mmol of (*Z*)-3-methylpent-2-en-4-yn-1-ol **1a** in the presence of 0.01 mmol of $RuCl_2(PPh_3)$(*p*-cymene) as catalyst precursor, without solvent at 60 °C for 2 h, led to the quantitative conversion into 2,3-dimethylfuran **2a** isolated in 74% yield (Scheme 1). Analogously, furans **2b** and **2c** were isolated in 50 and 85% respective yields from **1b** and **1c**. This reaction corresponds to the intramolecular addition of the OH group at the internal carbon of the triple bond to specifically afford 2-methylfuran derivatives. The reaction is specific to terminal alkynes since no conversion was observed when (*Z*)-3-methylhex-2-en-4-yn-1-ol [MeC≡C–C(Me)=CH–CH_2OH] was treated under similar conditions.

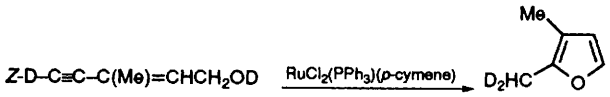
Starting from **1a'** containing deuterium in both hydroxy and terminal alkyne groups, the same reaction led to a complete conversion into furan **2a'** and the two deuterium atoms were incorporated into the methyl group of the furan attached to C(2). From the (*E*)-3-methylpent-2-en-4-yn-1-ol isomer, no cyclization reaction was observed, which indicated that this ruthenium-catalysed isomerization is specific of (*Z*)-enynols of type **1**.



1a–c **2a–c**

a, R = H, 60 °C; **b**, R = Et, 60 °C; **c**, R = Ph, 100 °C

Scheme 1



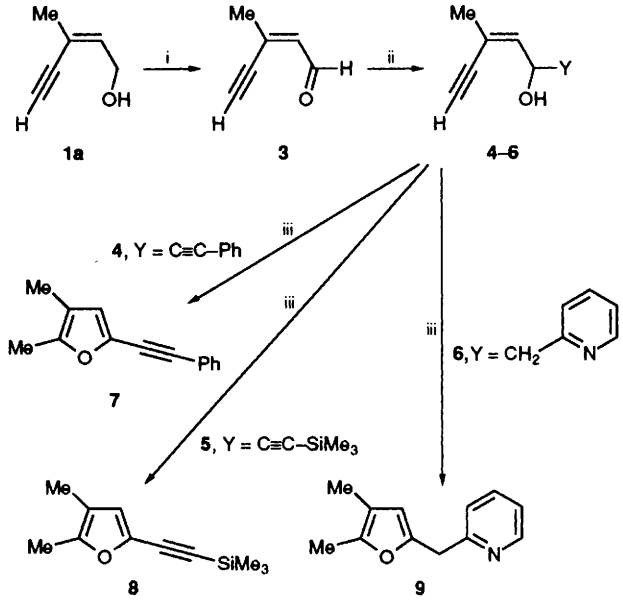
1a **2a'**

The generality of this novel reaction was demonstrated by the synthesis of a variety of substituted furans from the secondary alcohols **4** and **5** containing fragile alkynyl substituents, and **6** containing a pyridine group. Since the *Z* geometry of the starting substrate was necessary, we have prepared various (*Z*)-2-en-4-yn-1-ols in two steps from the commercially available compound **1a** by oxidation into the (*Z*)-aldehyde **3** followed by condensation with a lithium derivative according to Scheme 2.

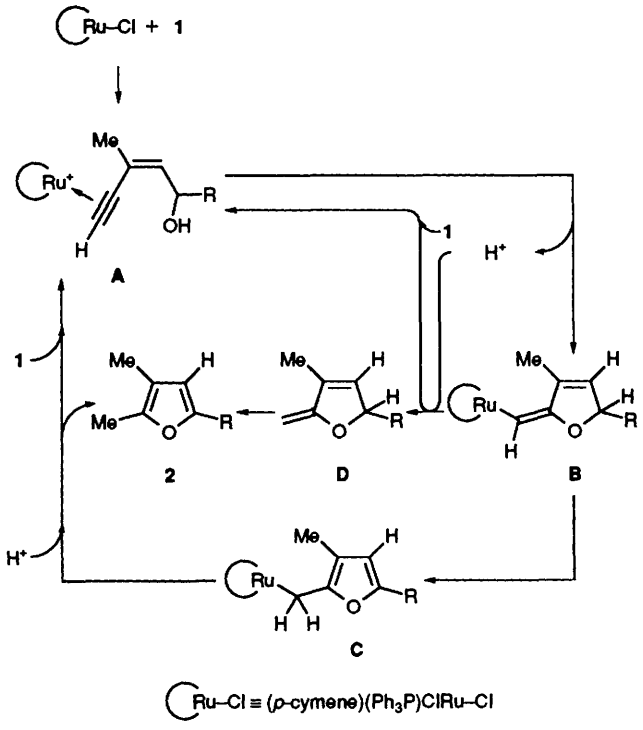
The cyclization of the (*Z*)-enynols **4–6** bearing a bulkier substituent than **1a–b** at C(1) was achieved in toluene, but an efficient cyclization could only be obtained when the reaction temperature was raised to 110 °C. Thus, the 5-alkynyl furans **7** was obtained from **4** in 53% yield after 2 h at 110 °C. These neutral conditions made possible the cyclization of the (*Z*)-enynol **5** containing a base-sensitive trimethylsilylalkynyl group into the furan **8** (11 h, 53%) without C–Si bond cleavage. The furanyl pyridyl methane derivative **9**, a potential chelating functional ligand, was obtained in three steps from the commercially available (*Z*)-enynol **1a** and 2-methylpyridine, *via* cyclization of **6** at 110 °C for 4 h (65%).

The mechanism of the above reaction may involve an electrophilic activation of the terminal triple bond by the ruthenium complex as already proposed for the addition of nucleophiles to alkynes.[11] The key steps of this isomerization are the intramolecular addition of the hydroxy group at the internal carbon of the η^2-coordinated triple bond in **A**, and a proton transfer to produce a stabilized aromatic five-membered furan ring (Scheme 3).

According to the relative rates of the reductive elimination and the proton migration, the formation of the furan ring may take place either on the coordinated ligand (**B** → **C**) or from



Scheme 2 *Reagents and conditions*: i, pyridinium chlorochromate, 0 °C; ii, YLi; H_2O–NH_4Cl; iii, 1 mol% $RuCl_2(PPh_3)$(*p*-cymene), toluene, 110 °C



Scheme 3

the organic methylidene intermediate **D** (**D** → **2**). The tautomerization of **A** into a vinylidene–ruthenium intermediate, as expected for related reactions,[11,12] does not occur since this pathway would lead to a never detected six-membered cyclic organic compound *via* nucleophilic attack of the alcohol at the more electrophilic terminal carbon of the η^1-vinylidene moiety.

The above reaction provides a novel ruthenium-catalysed route to functional furans from acetylenic alcohols. It takes place under neutral conditions and thus may find applications for the access to fragile biologically active substrates containing the furan structure. Whereas the presence of the methyl group at C(2) resulting from the transformation of the terminal end of the triple bond is compulsory, we have shown that functional substituents could be introduced at C(5).

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