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Synthesis of functionalised cyclopentenones via rearrangement of pyranones

Stephen Caddick,[a,*] Steven Cheung,[a] Lisa M. Frost,[a] Safraz Khan[a] and Garry Pairaudeau[b]

[a]*The Chemistry Laboratory, University of Sussex, Falmer, Brighton BN1 9QJ, UK*
[b]*Department of Medicinal Chemistry, AstraZeneca R & D Charnwood, Bakewell Rd, Loughborough LE11 5RH, UK*

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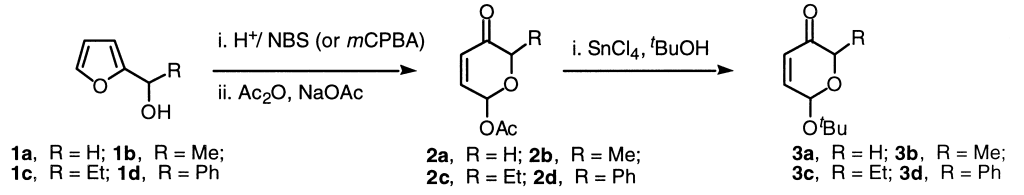
Abstract

Substituted functionalised cyclopentenones could be obtained via base-mediated isomerisation of pyranones.

Keywords: pyranone; cyclopentenone; rearrangement; isomerisation.

During our investigation into the dienediyne anticancer antibiotics[1] we required a practical synthetic approach to functionalised cyclopentenone derivatives. We were particularly attracted to a seminal report which showed the isomerisation reaction of a pyranone to a dihydroxylated cyclopentenone derivative.[2] We were able to devise a modified procedure, which could be carried out on preparative scale (ca. 30 g) without the requirement of metal catalysts using only an amine base.[3] In this report we make observations on this isomerisation reaction, and describe the synthesis and isomerisation of C-2 substituted pyranones.

Pyranones **3** can be prepared from furan derivatives **1** using the sequence shown below,[4] which can be carried out on large scale (50–100 g scale, Scheme 1).



Scheme 1.

* Corresponding author.

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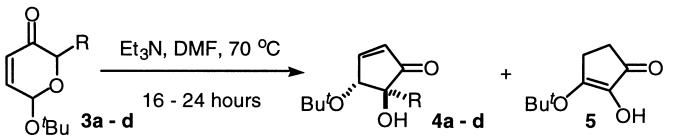
A study on the rearrangement of pyranones **3** is presented in Table 1. Our early work on the parent pyranone **3a** is noteworthy because it can deliver good quantities of substituted cyclopentenones under basic conditions (entry 1). Intriguingly, the conditions used are reminiscent of those used by a number of workers to generate oxidopyrilium species from related acetoxy pyranone derivatives (i.e. **2**).[5] It is clear that the reactivity of a pyranone is sensitive to substrate structure and/or reaction conditions. Consistent with this hypothesis is our finding that the nature of the amine base can have a profound and detrimental impact on the reactivity of pyranone **3a** (entries 2, 3). Further to this observation is that solvent can affect the reaction and we discovered that performing the reaction in methanol led to the isolation of product **5** (entry 4), which we assume is derived from isomerisation of the initially formed cyclopentenone **4a**. In order to further support this assumption we stirred cyclopentenone **4a** with Et_3N and obtained **5** (entry 5). In order to extend this methodology we embarked upon a study on the isomerisation of C-2 substituted pyranone derivatives **3b–d**. We felt that this would be a considerable test of our protocol, particularly in view of the lack of similar transformations in the literature. Indeed the early report describing related work suggested that isomerisation of this type could not be extended to C-2 substituted pyranones.[2] In agreement with these early reports we found that the isomerisation of precursors **3b–d** were disappointing; despite numerous attempts we were unable to promote efficient isomerisation using standard base, DMF reaction conditions (entries 6, 7 and 8). However, we were delighted to find that simply changing from DMF to MeOH as the reaction solvent gave the isomerisation products **4b–d** in moderate to good yield (entries 9–11).

Table 1
Base-mediated isomerisation reaction of substituted pyranones



Entry	*R*	*Reaction Conditions*	*Yield/ %*
1	H (**3a**)	NEt_3 /DMF /Δ /24 h	76 (**4a**)
2	H (**3a**)	$^iPr_2NEt$ /DMF /Δ/ 24 h	29 (**4a**)
3	H (**3a**)	Pyridine /DMF /Δ/ 24 h	11 (**4a**)
4	H (**3a**)	NEt_3 /MeOH /Δ /24 h	21 (**5**)
5	H (**4a**)	NEt_3 /MeOH /Δ /24 h	37 (**5**)
6	Me (**3b**)	NEt_3 /DMF /Δ /24 h	0 (**4a**)
7	Et (**3c**)	NEt_3 /DMF /Δ /24 h	29 (**4c**)
8	Ph (**3d**)	NEt_3 /DMF /Δ /7 h	6 (**4d**)
9	Me (**3b**)	NEt_3 /MeOH /Δ /24 h	56 (**4b**)
10	Et (**3c**)	NEt_3 /MeOH /Δ /48 h	37 (**4c**)
11	Ph (**3d**)	NEt_3 /MeOH /Δ /7 h	52 (**4d**)

One of the difficulties associated with developing this methodology is the characterisation of the isomerised products and the stereochemical outcome can only convincingly be corroborated using X-ray crystallography. We have confirmed the structure of **4b** by X-ray crystallography and by analogy we tentatively assign the other adducts as possessing the *trans* arrangement of the two-hydroxyl groups (Fig. 1).

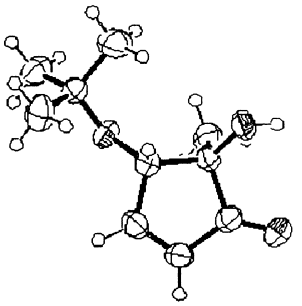
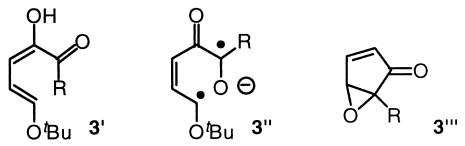


Figure 1. Cyclopentenone **4b**

In mechanistic terms one could envisage at least three distinct pathways for this transformation:

- cyclisation of an intermediate **3′** formed by electrocyclic ring opening of an enol derived from **3**;
- 1,2-Wittig rearrangement invoking biradical **3″**;[6] and
- cyclisation to give epoxide **3‴** followed by nucleophilic ring opening.[7]



Of these three possibilities the intermediate epoxide **3‴** is least likely given the success of the isomerisations in methanol. Further work will be required to further delineate the mechanistic features of this rearrangement.

In conclusion, we have shown that the appropriate choice of reaction condition can lead to base-mediated isomerisation of pyranones to cyclopentenones. We have shown that by careful choice of the reaction conditions we can extend this protocol to prepare C-2 substituted cyclopentenones which have not previously been synthesised and which have not previously been accessible using this or any other related methodologies.[8] The synthetic value of these highly functionalised cyclopentane derivatives is yet to be rigorously established. However, given the number of academic and industrially interesting cyclopentanoid compounds, we envisage this methodology finding application in synthesis.[9]

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