# Indirect Support for a Stepwise Carbonium Ion Pathway Operating in (4+3)-Cycloaddition Reactions between Furanoxonium Ions and 1,3-Dienes

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**Abstract:** Treatment of solutions of the furfuryl alcohol **6** in dichloromethane–methanol with buta-1,3-diene or cyclohexa-1,3-diene or with cyclopentadiene in the presence of trifluoroacetic acid leads to the corresponding substituted furyl tetrahydrofurans, **8**, **12** and **15** respectively, rather than to the products **10**, **13** and **16** anticipated from intermolecular (4+3)-type cycloaddition reactions. These outcomes provide indirect experimental support for a stepwise carbonium ion pathway operating in (4+3)-cycloaddition reactions between furanoxonium ions and 1,3-dienes. Alongside other results, the outcomes also highlight a limitation to (4+3) cycloadditions in cycloheptene ring synthesis when the precursors contain hydroxyl groups capable of intercepting any carbonium ion intermediates leading to O-heterocyclic by-products.

Key words: furfuryl alcohols, (4+3)-type cycloadditions, furanoxonium ions

Furfuryl alcohols 1 are readily available compounds and they have been used widely as starting materials in a myriad of synthetic transformations. For example, they show a high propensity to react with oxidants and also with acids leading to synthetically useful pyrylium and furanoxonium ion intermediates 2 and 3, respectively.<sup>1</sup> These intermediates then undergo novel [(5+2), (4+3)] and (4+2)] cycloaddition reactions with appropriate alkenes and 1,3-dienes leading to polycyclic ring systems, as found in some important biologically active natural products.<sup>2,3</sup> In earlier research we evaluated the scope for (4+3) and then (4+2) intramolecular cycloaddition reactions from appropriately substituted furanoxonium ion intermediates in approaches to the cycloheptene and cyclohexene ring-containing natural products, rameswaralide (4) and plumarellide (5), respectively (Figure 1).<sup>4,5</sup> Although we initially represented these separate furanoxonium ion cycloaddition reactions as (4+3) or (4+2) processes, subsequent synthetic work accompanied by density functional theory (DFT) calculations, first by Winne et al.<sup>6</sup> and then by ourselves, have given credence to the notion that the cycloadditions are more likely to be stepwise processes involving discrete carbonium ion intermediates.<sup>7</sup> We have now taken the opportunity to examine the likelihood of carbonium ion intermediates in the aforementioned (4+3) cycloaddition reactions leading to cycloheptenes, and studied the acid-catalysed addition reactions between 1,3-dienes and furfuryl alcohols which

*SYNLETT* 2013, 24, 2720–2722 Advanced online publication: 14.10.2013 DOI: 10.1055/s-0033-1339893; Art ID: ST-2013-D0816-L © Georg Thieme Verlag Stuttgart · New York incorporate additional juxtaposed hydroxyl substituents. We anticipated that these hydroxyl groups would intercept any carbonium ion intermediates produced during any addition reactions between the starting materials, and thus inhibit the formation of products resulting from (4+3)-type cycloaddition reactions. The outcome of this premise is presented here.





We first examined the reactivity of the vicinal diol-based furfuryl alcohol  $6^8$  with buta-1,3-diene in the presence of trifluoroacetic acid (TFA) in dichloromethane-methanol.9 Whatever the mechanism, that is, a concerted reaction or a stepwise carbonium ion process, with no intervention by the additional tertiary hydroxyl group in 6, the anticipated product from this reaction would be the furan ring-fused cycloheptene 10 resulting from an intermolecular (4+3)type cyclisation (Scheme 1). However, the product we obtained was the substituted furyl tetrahydrofuran 8 in a very good 75% yield. The structure and stereochemistry of the major diastereoisomer produced in the reaction (i.e., 8), followed from analysis of its relevant spectroscopic data. The new compound exhibited the expected molecular ion at m/z 287.1261 [M + Na]<sup>+</sup> in its high resolution mass spectrum, corresponding to the molecular formula  $C_{15}H_{20}O_4$ . The <sup>13</sup>C NMR spectrum showed signals for 15 carbon atoms, and the DEPT spectra revealed the presence of four methyl, two methylene, five methine and four quaternary carbons.



### Scheme 1

The presence of the carbon signal at  $\delta$  106.9 showing an HSQC correlation to the <sup>1</sup>H NMR resonance at  $\delta$  6.33 was indicative of a furan CH. Also of note were the carbon signals at  $\delta$  139.2 and  $\delta$  116.1 associated with proton resonances at  $\delta$  5.89 ( $\delta$  139.2),  $\delta$  5.27 and  $\delta$  5.12 ( $\delta$  116.1), with the proton signals showing coupling to each other, thus establishing the presence of the vinyl group in the new structure. The full structure was assigned following examination of COSY, HSQC and HMBC NMR spectra. In a similar manner, treatment of the same furfuryl alcohol 6 separately with cyclohexa-1,3-diene and cyclopentadiene under the same reaction conditions to those used with buta-1,3-diene led to the corresponding furyl tetrahydrofurans 12 (70%) and 15 (65%), respectively. We were not able to obtain any evidence for the co-formation of the products, 13 and 16 respectively, resulting from competing (4+3)-type cycloaddition reactions involving 6 and cyclohexa-1,3-diene or cyclopentadiene.

The production of the substituted tetrahydrofurans **8**, **12** and **15** from the aforementioned reactions with the furfuryl alcohol **6** result from initial formation of the corresponding allylic carbonium ion intermediates, **9**, **11** and **14**, respectively, produced from electrophilic substitution of the 1,3-dienes by the furfurylcarbonium/furanoxonium ion intermediate **7**. These allylic carbonium ion intermediates, **9**, **11** and **14** are then trapped by their proximate tertiary hydroxyl groups, leading to the observed substituted furyl tetrahydrofuran products (**8**, **12** and **15**). The

failure to observe formation of the compounds **10**, **13** and **16** in these reactions probably reflects the differing rates of oxygen-to-carbon over carbon-to-carbon bond formation from the common intermediates **9**, **11** and **14**, respectively. These outcomes therefore indirectly provide some useful experimental support for a stepwise carbonium ion pathway operating in intermolecular (4+3)-cycloaddition reactions between furanoxonium ions and 1,3-dienes.

In other studies, we examined the outcomes of the acidcatalysed reactions involving the furfuryl alcohols **6** and **22**,<sup>10</sup> and a selection of furans **17**, and the diene **20**. Thus, reaction between **6** and the furans **17** in dichloromethane– methanol in the presence of trifluoroacetic acid gave only the bis-furanmethyl substituted tertiary alcohols **18**, with no evidence of the co-formation of the products (e.g. **19**), anticipated from a (4+3)-type cycloaddition reaction (Scheme 2). The corresponding reactions between **6** and the diene **20**, and between the furfuryl alcohol **22** and buta-1,3-diene led, perhaps not unexpectedly, to the substituted dioxolane **21** and to the substituted tetrahydrofuran **23**, respectively.

In conclusion, our study has provided some support for a stepwise carbonium ion pathway operating in (4+3)-type intermolecular cycloaddition reactions between furanoxonium ions and 1,3-dienes leading to cycloheptene-ring synthesis, and has also highlighted a limitation to the same reactions.<sup>11</sup> Thus, when there are hydroxyl groups in the precursors in close proximity to any allylic (or other) car-



#### Scheme 2

bonium ion intermediates, these centres will inhibit the formation of any anticipated (4+3) cycloaddition products, at the expense of formation of O-heterocyclic byproducts.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (9) For a general experimental procedure for treatment of the vicinal diol based furfuryl alcohol 6 with TFA and a range of dienes, see the Supporting Information.
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