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Sequential isomerization and ring-closing metathesis: masked styryl and vinyloxyaryl groups for the synthesis of benzo-fused heterocycles

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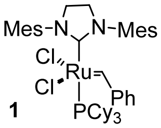
Abstract—The use of an aryl allyl ether and an arylallyl group as masked vinyl ether and 1-propenylphenyl groups for ring-closing metathesis (RCM) leading to the synthesis of benzo-fused heterocycles was demonstrated by using a ruthenium-mediated isomerization followed by a ruthenium-mediated RCM reaction. This resulted in the syntheses of a variety of products including two substituted benzo[1,4]dioxins, a naphtho[2,3-*b*][1,4]dioxin, a 2*H*-chromene and a benzo[*b*]furan.

The recent literature contains a myriad of examples of the application of ruthenium-mediated ring-closing metathesis (RCM).[1–5] The RCM catalyst of choice for this transformation is the Grubbs' second-generation catalyst **1** owing to its activity, stability and tolerance to various functional groups and solvent impurities.



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However, amongst the large numbers of examples described in reviews, very few utilize RCM for the metathesis of vinyl ether[6–8] or silyl enol ether[9,10] groups. RCM using Grubbs' catalysts on substrates containing electron-rich vinylic olefins are known to be problematic[7,8] and earlier this year we communicated the first examples of high-yielding metathesis reactions with aryl vinyl ethers (e.g. the conversion of precursor **2** into 4*H*-chromene **3**.)[11] Nishida and co-workers also recently published the related intramolecular RCM of substituted enamines **4** to give indoles **5** in excellent yields.[12] This paper has prompted us to divulge our successes in the RCM of other substrates containing electron-rich olefins. Furthermore, we demonstrate the in situ isomerization of aryl allyl ethers or arylallyl groups into aryl 1-propenyl ethers or 1-propenylbenzenes, respectively, prior to RCM. This strategy thus obviates the need to synthesize the required aryl vinyl ethers or styrenes directly, the synthesis of which can be problematic.

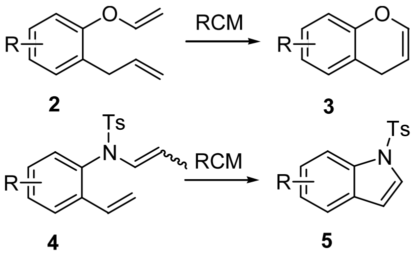

Figure 1.

1. Benzo[1,4]dioxins

Previously we have shown that as part of our ongoing interest in the synthesis of benzo-fused bicyclic molecules,[13–16] we were able to use RCM to synthesize 4*H*-chromenes, naphthols and indenols,[11] all of which are found as structural units in natural products. Firstly, following our success in accomplishing RCM on the vinyl ether-containing substrates, we decided to test the boundaries of this methodology by the intramolecular RCM of molecules containing aryl-bis-*O*-vinylic olefins. This would then give us benzo[1,4]dioxins,[17] which are interesting compounds with promising anti-tumour activity. Coudert has recently published an approach to their synthesis.[18] Our methodological approach is shown in the disconnection of compound **6** to the bis(vinyloxy)aryl precursors **7**.

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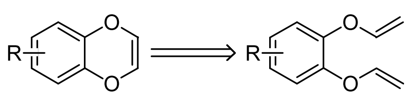
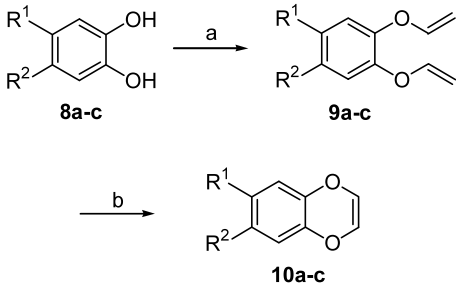


6 **7**

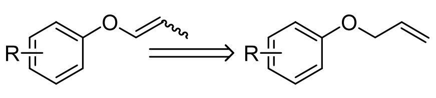
Three differently substituted catechols **8a–c** were subjected to vinylation with tetravinyltin and copper(II) acetate, according to a recently published procedure,[19] to afford the bis(vinyloxy) compounds **9a–e** in rather poor yields (Scheme 1).[20] These yields were lower than expected and we postulate that competing formation of copper–catechol complexes probably contributes to the limited success of the reactions. Furthermore in cases **8a** and **8b** the experiments were poorly reproducible and often gave complex mixtures of vinylated products. Only 2,3-bis(vinyloxy)naphthalene **9c** was easily isolated.[21,22] When it was treated with catalyst **1** under standard reaction conditions, the corresponding known compound, naphtho[2,3-*b*][1,4]dioxin **10c**, was produced.[18] To the best of our knowledge this is the first use of the RCM methodology to synthesize this class of compounds, and the first synthesis of the 1,4-benzodioxins by *direct* ring-closure methods.[17]



Scheme 1. **a**. $R^1,R^2=H$; **b**. $R^1=Me$, $R^2=H$; **c**. $R^1,R^2=$fused benzene ring. *Reagents and conditions*: For **c**. (a) $Cu(OAc)_2$, $Sn(vinyl)_4$, acetonitrile, O_2, rt, 47%; (b) 5% catalyst **1**, toluene, 67%, 70–80°C.

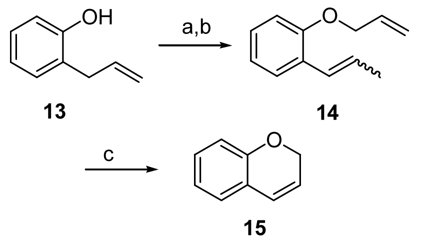
2. Isomerizations of arylallyl and aryloxyallyl groups followed by RCM

The *O*-vinylation reaction used above has the disadvantage of using stoichiometric amounts of copper acetate and an environmentally unfriendly, atom uneconomical tetravinylstannyl reagent. Thus, having experienced problems with the synthesis of the bis(vinyloxy) ethers in the synthesis of the benzo[1,4]dioxins, we decided to investigate an alternative approach. The isomerization of aryloxyallyl ethers has attracted significant attention in the last few years and several groups have used efficient transition metal catalysts to achieve this goal. Examples include the use of catalysts based on the metals ruthenium,[23] iridium[24] and rhodium.[25] Since phenols are easily *O*-allylated by well established methods to produce **11**, subsequent isomerization should provide a useful aryl vinyl ether **12** as depicted in the disconnection below. Compound **12** would then be available for ruthenium-mediated RCM.



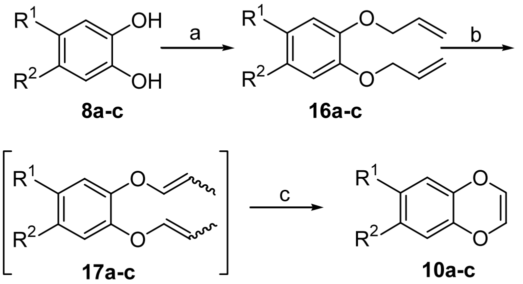
12 **11**

The first experimental sequence involved the isomerization of commercially available 2-allylphenol **13** with $[RuClH(CO)(PPh_3)_3]$.[23] This was followed by alkylation of the phenol with allyl bromide and K_2CO_3 to give **14** in excellent yield over two steps (Scheme 2). Subsequent treatment of this substrate with catalyst **1** then afforded 2*H*-chromene **15**[26] in excellent yield.[27] Other approaches to 2*H*-chromenes, of which abundant examples exist in Nature,[28] using ruthenium-mediated RCM have already been communicated.[29–32] However, the major difference in our work is that the intramolecular RCM occurred between an allyloxy substituent and a *styrene*. Using this ruthenium-catalyzed allyl/propenyl isomerization reaction therefore extends the substrates available in this approach as allyl groups *ortho* to a substituent on an aromatic ring are often easy to introduce, e.g. by Claisen rearrangement, Kumada coupling, directed *ortho*-metalation[33] and electrochemical coupling.[34]



Scheme 2. *Reagents and conditions*: (a) $[RuClH(CO)(PPh_3)_3]$ (1%), toluene, 80°C, 90%; (b) allyl bromide, K_2CO_3, acetone, reflux, 86%; (c) 5% catalyst **1**, $CDCl_3$, rt, >80% (by ^1H NMR spectroscopy).

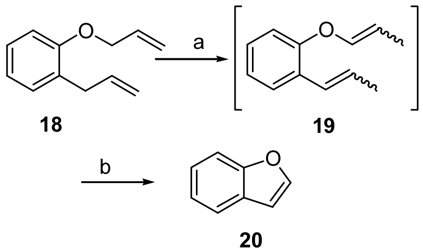
In addition, synthesis of benzo[1,4]dioxins was more readily accomplished using our new allylation/isomerization/RCM procedure. Bis(*O*-allylation) of catechols **8a–c** afforded compounds **16a–c** in good yields (Scheme 3). This was then followed by in situ isomerization as described before to afford the aryl bis(vinyl) ethers **17a–c**. The formation of the product was monitored by ^1H NMR spectroscopy and the acid-sensitive enol ether intermediates **17** were not isolated. Grubbs' catalyst **1** was then added directly to the reaction mixture, and the desired benzo[1,4]dioxins **10a–c** were obtained in good yields.[27] Other reported examples of 'one-pot' multistep reactions featuring RCM include RCM/hydrogenation[11,35] and RCM/isomerization[36,37] sequences. We have thus been successful in synthesizing compounds with the benzo[1,4]dioxin structure using a simple three-step two-reaction process. The desired compounds were readily formed and this methodology should stimulate further exploration of the properties of this class of organic molecules.



Scheme 3. **a**. R^1,R^2 = H; **b**. R^1 = Me, R^2 = H; **c**. R^1,R^2 = fused benzene ring; *Reagents and conditions*: (a) allyl bromide, K_2CO_3, acetone, reflux, **16a** 76%, **16b** 93%, **16c** 96%; (b) [RuClH(CO)(PPh_3)$_3$] (1%), toluene-d_8, 80°C (complete by ^{1}H NMR spectroscopy); (c) 5% catalyst **1**, toluene-d_8, yields over two steps: **10a**[38] >70% (by ^{1}H NMR spectroscopy), **10b**[39] >70% (by ^{1}H NMR spectroscopy, isolated yield after chromatography 58%), **10c**[18] >90% (by ^{1}H NMR spectroscopy).

Finally, we decided to further extend our novel one-pot isomerization/RCM reaction. 2-Allylphenol was thus converted into allyl-2-(allyloxy)benzene **18** under standard conditions. [RuClH(CO)(PPh_3)$_3$] was then added to a solution of **18** in benzene-d_6 or toluene-d_8 and the reaction mixture was heated at 60–80°C for 18 h (Scheme 4). Analysis by ^{1}H NMR spectroscopy confirmed that the isomerization of both allyl substituents had occurred to afford the acid-labile compound **19** which was not isolated. The introduction of catalyst **1** then readily afforded the benzo[*b*]furan **20**[40] in excellent conversion as determined by further ^{1}H NMR spectroscopy.[27] This result constitutes a novel approach to the ubiquitous benzo[*b*]furan skeleton[41] and parallels Nishida's approach[12] to indoles as depicted in Figure 1. The methodology once again utilizes readily accessible starting materials, and work is now in progress to demonstrate the general applicability of this approach.

In conclusion, we have shown that the versatile RCM reaction with ruthenium catalyst **1** can be applied to substrates containing electron-rich aryl 1,2-bis(vinyloxy) substituents to afford benzo[1,4]dioxins. Furthermore we have demonstrated that the aryloxyallyl and arylallyl groups can function as masked aryl vinyl ethers and 1-propenylbenzenes, respectively, which readily undergo ruthenium-mediated RCM reactions.[42] We are currently extending this work to the synthesis of natural products and other interesting systems.



Scheme 4. *Reagents and conditions*: (a) [RuClH(CO)(PPh_3)$_3$] (1%), benzene-d_6 or toluene-d_8, 90–100°C (complete by ^{1}H NMR spectroscopy); (b) 5% catalyst **1**, CH_2Cl_2, 60–70°C >80% over two steps (by ^{1}H NMR spectroscopy).

Acknowledgements

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39. 6-Methylbenzo[1,4]dioxin **10b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.18 (3H, s, $ArCH_3$); 5.84 (2H, s, 2×OCH); 6.44 (1H, br s, 5-H); 6.49 (1H, d, $J=8.1$, 8-H); 6.60 (1H, dd, $J=8.1$ and 1.2, 7-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.3; 115.8; 116.8; 124.3; 126.6; 126.8; 134.0; 140.3; 142.2.
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