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Synthesis of 2*H*-1,5-benzodioxepin and 2,5-dihydro-1,6-benzodioxocin derivatives via ring-closing metathesis reaction

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Abstract—The synthesis of various 2*H*-1,5-benzodioxepin and 2,5-dihydro-1,6-benzodioxocin derivatives is described. The key step involves the construction of seven- and eight-membered rings via ring-closing metathesis reaction.

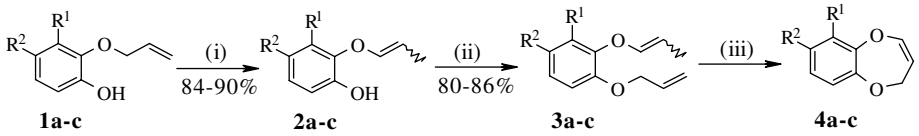
The past few years have seen an intense interest in the ring-closing metathesis (RCM) reaction. This type of carbon–carbon bond formation has proven to be a very powerful method for the synthesis of cyclic systems.[1–5]

However, amongst the large number of examples described in reviews, relatively few utilise RCM for the synthesis of benzo-fused bicyclic molecules.[6–11] As part of our ongoing interest in the synthesis of this class of compounds, in particular substrates containing electron-rich olefins such as benzodioxins[12] and benzodioxepins,[13] we report here our preliminary results on a general approach to a range of benzo-fused bicyclic molecules using first- and second-generation Grubbs' catalysts **I** [$(PCy_3)_2Cl_2Ru{=}CHPh$] and **II** [$(IMesH_2)(PCy_3)Cl_2Ru{=}CHPh$],[14] respectively, in the key ring-closing step.

Very recently, van Otterlo et al. showed that the versatile RCM reaction with ruthenium catalyst **II** can be applied to 1,2-bis(vinyloxy)benzenes to afford benzo[1,4]dioxins.[15] They also described the synthesis of a series of *N*- and *O*-benzo-fused heterocycles using a ruthenium-mediated isomerisation followed by RCM.[16] This paper prompted us to disclose our success in the RCM of other substrates containing electron-rich olefins. Using simple precursors, we were able to synthesise benzodioxepin and benzodioxocin derivatives.

1,5-Benzodioxepins: Although the 2*H*-1,5-benzodioxepin ring system constitutes a common structural element in some natural products[17] and is a similar feature to that found in the antifungal Strobilurin G,[18] the synthesis of this type of molecules is rarely cited in the literature.

In continuation of our longstanding interest in the preparation of fused oxygenated ring, we report an interesting and efficient synthetic approach towards 1,5-benzodioxepin compounds as illustrated in Scheme 1.



Scheme 1. (**a**) $R^1 = R^2 = H$; (**b**) $R^1 = OMe$, $R^2 = H$; (**c**) $R^1 = H$, $R^2 = Br$. Reagents and conditions: (i) *t*-BuOK, DMSO, rt, 6 h; (ii) allyl bromide, K_2CO_3, acetone, reflux, 10 h; (iii) catalyst (mol%) **I** or **II** (see Table 1), C_6H_6, 55 °C.

Keywords: 2*H*-1,5-Benzodioxepin; 2,5-Dihydro-1,6-benzodioxocin; Ring-closing metathesis.
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The starting materials, phenols **1a** and **1b**,[19] were synthesised by *O*-alkylation of the appropriate diols **5a** and **5b** with 1 equiv of allyl bromide in the presence of K_2CO_3 in acetone at reflux, in 70% and 72% yield, respectively. Compound **1c** was obtained from 4-bromo-2-(allyloxy)acetophenone[20] by Baeyer–Villiger oxidation followed by hydrolysis with aqueous NaOH 5% in ethanol.

Isomerisation[21] of phenols **1a–c** was carried out by treatment with 8 equiv of *t*-BuOK in DMSO for 6 h at room temperature to give phenols **2a–c** in 84–90% yield as a mixture of *E*- and *Z*-isomers. Subsequent treatment of these substrates with 1 equiv of allyl bromide in the presence of potassium carbonate in acetone at reflux afforded compounds **3a–c** in excellent yield.

The treatment of **3a** and **3c** gave no cyclised products with catalyst **I**. In contrast, in the presence of catalyst **II** (10%), the reaction proceeded smoothly (in 6 h) to give **4a**[22] and **4c** in 53% and 82% yield, respectively. However, cyclisation of **3b** via RCM in the presence of catalyst **I** (20%) for 17 h afforded **4b** in 80% yield, while the use of catalyst **II** (10%) for 6 h increased the yield to 98% (Table 1).

These results constitute a novel approach for the synthesis of the 1,5-benzodioxepin structure using an allylation/isomerisation/RCM procedure. The desired compounds were readily formed and this methodology should stimulate further exploration of the properties of this class of organic molecules. To the best of our knowledge, this study represents the first use of RCM to synthesise benzodioxepin derivatives.

1,6-Benzodioxocins: The eight-membered ring analogues are also interesting and show potential pharmacological activity[23] and industrial applications.[24] So far, to the best of our knowledge, only a few reports describe the synthesis of 2,5-dihydro-1,6-benzodioxocin. Schroth[25] disclosed the first route to this eight-membered ring system using catechol and *cis*-1,4-dichloro-2-butene in 35–40% yield. However, this method has some limitations since an inseparable side product is formed along with the low yield of the desired compound. Recently, Grubbs[26] and Sarkar[27] accessed this ring system using RCM reaction using elaborate ruthenium catalysts. Unfortunately only one benzodioxocin derivative was described and the ruthenium catalysts used are not commercially available. Later, König[28] reported the synthesis of this eight-membered ring systems via an RCM reaction of 1,2-dihydroxybenzene diallyl ether **6a** using Grubbs' catalyst **I**. However, a mixture of cyclic and acyclic products was obtained in an overall yield of only 35%.

Table 1. Synthesis of 2*H*-1,5-benzodioxepin derivatives **4a–c**

Substrate	Catalyst (mol%)	Time (h)	Product	Yield[a] (%)
3a	**I** (10)	17	**4a**	—[b]
3a	**II** (10)	6	**4a**	53[c]
3b	**I** (20)	17	**4b**	80
3b	**II** (10)	6	**4b**	98
3c	**I** (10)	17	**4c**	—[b]
3c	**II** (10)	6	**4c**	82

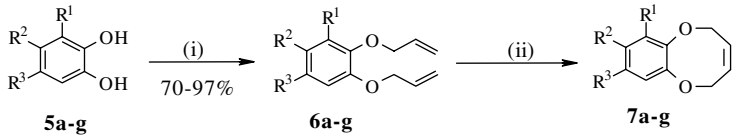
[a] Yield in isolated product after silica gel chromatography.
[b] The starting material **3a** or **3c** was recovered.
[c] The low yield is due to the lower reactivity of substrate **3a**.

In the present work, we report our initial investigations on the application of RCM with catalysts **I** or **II** as the key cyclisation step in the synthesis of benzodioxocin derivatives. Our strategy is based on the preparation of various 1,2-diallyloxybenzenes **6a–f** and 2,3-diallyloxynaphthalene **6g** by alkylation of phenols **5a–f** and naphthol **5g** followed by the cyclisation of these compounds under the RCM conditions.

The ethers **6a–g** were obtained by treatment of the appropriate diols **5a–g** with 2 equiv of allyl bromide in the presence of K_2CO_3 in acetone at reflux (Scheme 2). The key metathesis reaction was carried out by varying different parameters such as quantity of catalyst, solvent, reaction time and temperature. After screening several reaction conditions, we found that the cyclisation forming the eight-membered rings **7a–g**[22] is possible by using various proportions of commercially available Grubbs' catalyst **I** at 55 °C in benzene.

It is interesting to point out that the quantity of catalyst and the time of reaction depend on the substrate. In the cases of **6d** and **6e**, an almost 2-fold ratio of catalyst **I** (15%) was necessary to reach completion of the reaction. Also, we have noted that the RCM of compounds **6a** and **6g** was even slower and required a higher amount (20%) of catalyst **I** to complete the reaction whereas, only 10% of catalyst **II** was required to produce **6a** in 60% yield (Table 2). In contrast, we found that 8% of catalyst **I** was sufficient to complete the RCM reaction of **6b**, **6c** and **6f** in satisfactory yield.

In summary, we have successfully applied the RCM reaction using the commercially available Grubbs' catalysts **I** and **II** to prepare a diversity of 2*H*-1,5-benzodioxepins and 2,5-dihydro-1,6-benzodioxocins in good yield. In these reactions, Grubbs' ruthenium carbene



5a-g **6a-g** **7a-g**

Scheme 2. (**a**) $R^1 = R^2 = R^3 = H$; (**b**) $R^1 = OMe$, $R^2 = R^3 = H$; (**c**) $R^1 = H$, $R^2 = NO_2$, $R^3 = H$; (**d**) $R^1 = H$, $R^2 = Br$, $R^3 = H$; (**e**) $R^1 = H$, $R^2 = CHO$, $R^3 = H$; (**f**) $R^1 = F$, $R^2 = R^3 = H$; (**g**) $R^1 = H$, R^2, R^3 = fused benzene ring. Reagents and conditions: (i) allyl bromide, K_2CO_3, acetone, reflux, 18–24 h; (ii) catalyst (mol%) **I** or **II** (see Table 2), C_6H_6, 55 °C.

Table 2. Synthesis of 2,5-dihydro-1,6-benzodioxocin derivatives **7a–g**

Substrate	Catalyst (mol%)	Time (h)	Product	Yield[a] (%)
6a	**I** (20)	17	**7a**	50[b]
6a	**II** (10)	17	**7a**	60
6b	**I** (8)	17	**7b**	68
6c	**I** (8)	12	**7c**	71
6d	**I** (15)	17	**7d**	69
6e	**I** (15)	17	**7e**	62
6f	**I** (8)	12	**7f**	70
6g	**I** (20)	17	**7g**	56[b]

[a] Yield in isolated product after silica gel chromatography.
[b] The low yields are due to lower reactivity of the substrates **6a** and **6g**.

complex **II** shows enhanced RCM activity compared to its parent **I**.

References and notes

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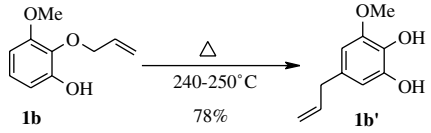
19. The determination of the structure of **1b** was ensured by transforming **1b** into **1b′** via Claisen and Cope rearrangements. We observed, in particular, the disappearance of coupling between of H_4 and H_6. 2D RMN experiments (HMBC, HMQC) of compound **4b** confirmed the structure of **1b**.



1b **1b'**

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22. All new compounds were fully characterised and gave satisfactory spectroscopic data. A representative example, 2*H*-1,5-benzodioxepin **4a**: **3a** (1.05 mmol) in C_6H_6 (5 mL) was added to a solution of 10 mol% catalyst **II** in CH_2Cl_2. The reaction mixture was stirred at 55 °C for 6 h. The pure **4a** was obtained by flash chromatography (AcOEt/petroleum, 1:9) in 53% yield. ^1H NMR ($CDCl_3$, 250 MHz) δ 4.56 (dt, 2H, $J = 1.9$, 4.0 Hz, C**H**$_2$CH=CH), 4.85–5.00 (m, 1H, CH_2C**H**=CH), 6.50 (dt, 1H, $J = 2$, 7.3 Hz, CH_2CH=C**H**), 6.95–7.15 (m, 4H, H_{arom}). MS (m/z) 149 (M+1). A representative example, 7-methoxy-2,5-dihydro-1,6-benzodioxocin **7b**: following the procedure described for **4a** but substituting catalyst **II** by 8 mol% catalyst **I** gave **7b** in 68% yield. ^1H NMR ($CDCl_3$, 250 MHz) δ 3.84 (s, 3H, OCH_3), 4.88 (d, 2H, $J = 3.1$ Hz, C**H**$_2$–CH=CH), 5.00 (d, 2H, $J = 6.0$ Hz, C**H**$_2$–CH=CH), 5.80–5.98 (m, 2H, CH_2–C**H**=C**H**), 6.50–6.60 (m, 2H, H_{arom}), 6.92 (t, 1H, $J = 8.3$ Hz, H_{arom}); MS (m/z) 193 (M+1).
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