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Isomerization and ring-closing metathesis for the synthesis of 6-, 7- and 8-membered benzo- and pyrido-fused *N*,*N*-, *N*,*O*- and *N*,*S*-heterocycles

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Abstract—An isomerization–ring-closing metathesis (RCM) strategy afforded *N*-substituted 4*H*-1,4-benzoxazines from the protected *N*-allyl-2-(allyloxy)anilines. In addition, RCM was used to synthesize the *N*-substituted, 8-membered benzo-fused heterocycles from the respective diallyl compounds: 1,2,5,6-tetrahydro-1,6-benzodiazocine, 5,6-dihydro-2*H*-1,6-benzoxazocine, 5,6,9,10-tetrahydropyrido[2,3-*b*][1,4]diazocine and 5,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide. The isomerization–RCM approach also afforded the 7-membered ring system, 2,5-dihydro-1,5-benzothiazepine 1,1-dioxide, from the protected *N*-allyl-2-(allylsulfonyl)-aniline. Furthermore, the structure of 1,6-bis[(4-methylphenyl)sulfonyl]-1,2,5,6-tetrahydro-1,6-benzodiazocine was confirmed by a single crystal X-ray determination.

1. Introduction

Ring-closing metathesis has seen a tremendous increase in synthetic applications over the last decade. The number of recent reviews covering this topic signifies that this reaction has become a valuable synthetic method for forming cyclic systems.[1] Our research group has been involved in the application of RCM to the synthesis of benzo-fused bicyclic molecules[2] in particular. Recently we have reported the use of a novel one-pot isomerization–RCM strategy to afford a number of these compounds, including the substituted benzodioxene **1**, dihydroisoquinoline **2** and benzofuran **3** as shown in Figure 1.[3] Although the number of examples in the literature describing isomerization reactions followed by RCM are limited,[3,4] this concept has been included in an in-depth review.[5]

In recent years several research groups have reported RCM approaches to benzo-fused 8-membered heterocycles.[6] These types of bicyclic molecules are potential pharmacological scaffolds with interesting biological activities.[7] An interesting paper by Guillaumet and coworkers highlighted their approach to the 2*H*-1,5-benzodioxepin and 2,5-dihydro-1,6-benzodioxocin skeletons utilizing a RCM approach.[8] This paper prompted us to publish the successes we have enjoyed in our laboratories concerning the syntheses of *N*,*N*-, *N*,*O*- and *N*,*S*-6-, 7- and 8-membered benzo-fused heterocycles using RCM and isomerization–RCM strategies.[9]

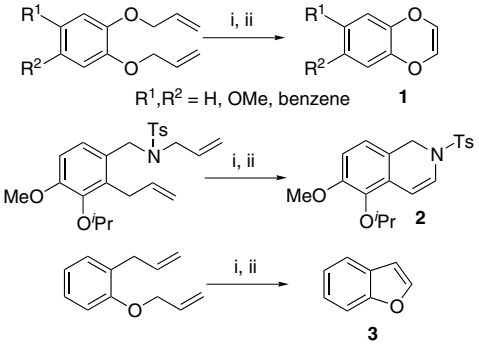

Figure 1. Examples of the application of an isomerization–RCM strategy: (i) isomerization and (ii) RCM.

Keywords: Isomerization; Ring-closing metathesis; Benzo-fused heterocycles; 1,4-Benzoxazines; 1,6-Benzodiazocine; 1,6-Benzoxazocine; 1,6-Benzothiazocine; 1,5-Benzothiazepine.
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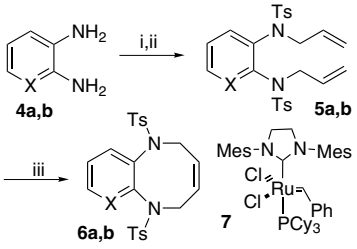
2. *N*-Substituted 1,2,5,6-tetrahydro-1,6-benzodiazocines and 5,6,9,10-tetrahydropyrido[2,3-*b*][1,4]diazocine

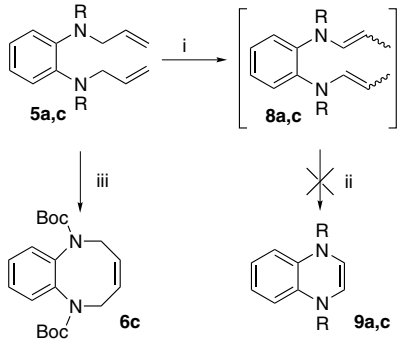
o-Phenylenediamine **4a** (X = CH) and 2,3-diaminopyridine **4b** (X = N) were initially protected as their bis-(4-methylphenyl)-sulfonamides. These compounds were then alkylated with an excess of allyl bromide and K_2CO_3 to afford compounds **5a** and **5b** in acceptable yields (Scheme 1). Subsequent treatment of these substrates with Grubbs' second generation catalyst **7** gratifyingly afforded the 8-membered 1,6-benzo-**6a**[10] and 1,6-pyrido-diazocine **6b**[11] ring systems in excellent yield.[12] Furthermore, to confirm the structure of product **6a** unambiguously, a single crystal X-ray structural determination was performed (see Fig. 2).[13]

At this point we attempted to use the isomerization–RCM approach that we have successfully applied to the synthesis of dioxenes.[3a] To this end, treatment of diallyl compound **5a** (X = CH) with the isomerization catalyst $[RuClH(CO)(PPh_3)_3]$[14,15] afforded the isomerized compound **8a**, which was not isolated (Scheme 2). However, much to our disappointment, treatment of **8a** with catalyst **7** did not afford the expected 1,4-dihydroquinoxaline **9a** and only starting material was recovered.

We wondered if the steric size of the two tosyl groups was preventing the two enamines in **8a** from reacting in a metathetic manner. To investigate this proposal the Boc-protected analogue of **4a** was synthesized and allylated to afford compound **5c** (56% over two steps from **4a**). This compound was exposed to $[RuClH(CO)(PPh_3)_3]$ and readily underwent the bis-isomerization process to give compound **8c** (Scheme 2). However, when this compound was subjected to catalyst **7**, no RCM process was evident from TLC analysis of the reaction mixture. Treatment of **5c** with catalyst **7**, however, once again readily afforded the 8-membered benzo-fused compound **6c** in a yield of 64%.



Scheme 1. Reagents and conditions: (i) TsCl, pyridine, 60 °C, N_2, 20–23 h; (ii) K_2CO_3, allyl bromide, acetone, 60 °C, N_2, 20–23 h, **5a**, X = CH (44% over two steps), **5b**, X = N (24% over two steps); (iii) 5% catalyst **7**, toluene, N_2, 5 h, rt, **6a**, X = CH (96%), **6b**, X = N (94%).



Scheme 2. Reagents and conditions: (i) for R = Ts: 5% $[RuClH(CO)(PPh_3)_3]$, d_8-toluene, 105 °C, N_2, 3–4 h (**8a** observed by NMR spectroscopy but not isolated), for R = Boc: 4% $[RuClH(CO)(PPh_3)_3]$, toluene, 95 °C, N_2, 98 h (96%); (ii) for R = Ts: 5% catalyst **7**, toluene, 110 °C, 5 h (only compound **8a** recovered), for R = Boc: 2 × 5% catalyst **7**, toluene, 80 °C, 18 h (only compound **8c** recovered in 63%); (iii) 5% catalyst **7**, toluene, 110 °C, N_2, 3 h (64%).

3. *N*-Substituted 5,6-dihydro-2*H*-1,6-benzoxazocines and 4*H*-1,4-benzoxazines

We also decided to synthesize the *N*,*O*-diallyl compound analogous to **5a** to test whether this compound would undergo the isomerization–RCM sequence. 2-Aminophenol **10** was therefore protected as its bis-tosyl equivalent to afford compound **11a** (Scheme 3). The phenolic tosyl group was then selectively hydrolyzed using a literature procedure[16] and the resultant compound was then allylated to give product **12a** in excellent yield. Once again the isomerization catalyst $[RuClH(CO)(PPh_3)_3]$ proved highly successful in mediating the bis-isomerization to afford compound **13a** in quantitative yield. Satisfyingly, addition of Grubbs' second generation catalyst **7** to compound **13a** cleanly afforded the substituted 4*H*-benzo[1,4]oxazine **14a**[17] in high yield.[18] RCM using Grubbs' catalysts on substrates containing electron-rich vinylic olefins is known to be potentially problematic[2a]

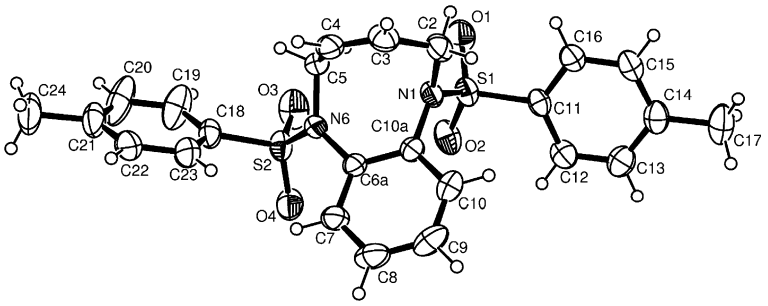
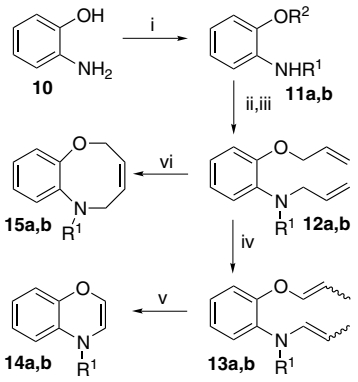
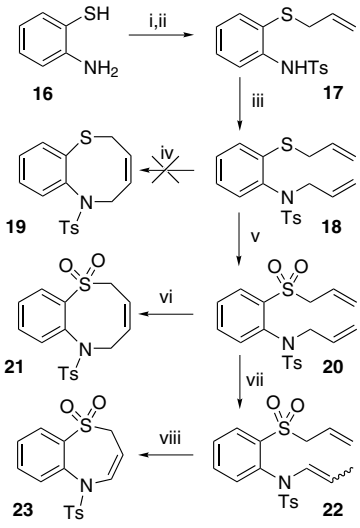


Figure 2. ORTEP diagram of the X-ray crystal structure of compound **6a** with thermal ellipsoids at 50% probability.



Scheme 3. Reagents and conditions: (i) for R^1, R^2 = Ts: TsCl, pyridine, 60 °C, N_2, 20–23 h, **11a** (87%); for R^1 = Boc and R^2 = H: Boc_2O, THF, rt, N_2, 12 h, **11b** (64%); (ii) for R^1, R^2 = Ts: Mg, MeOH, rt, 8 h (93%); (iii) K_2CO_3, allyl bromide, acetone, 60 °C, N_2, 18 h, **12a** (99%), for R^1 = Boc: K_2CO_3, allyl bromide, acetone, 60 °C, N_2, 23 h, **12b** (92%); (iv) for R^1 = Ts: 1% [RuClH(CO)(PPh_3)$_3$], toluene, 95 °C, N_2, 2 h, **13a** (quantitative), for R^1 = Boc: 3% [RuClH(CO)(PPh_3)$_3$], d_8-toluene, 95 °C, N_2, 98 h, **13b** (quantitative by NMR spectroscopy, 81% isolated); (v) for R^1 = Ts: 5% catalyst **7**, toluene, 45 °C, N_2, 2.5 h, **14a** (90%), for R^1 = Boc: 2 × 5% catalyst **7**, toluene, 60 °C, N_2, 24 h, **14b** (71%); (vi) 5% catalyst **7**, toluene, rt, N_2, 5 h, **15a**, R^1 = Ts (69%), **15b**, R^1 = Boc (70%).



Scheme 4. Reagents and conditions: (i) allyl bromide, MeOH, NaOH, H_2O, rt, 2 h; (71%); (ii) TsCl, pyridine, CH_2Cl_2, 45 °C, N_2, 24 h (97%); (iii) K_2CO_3, allyl bromide, acetone, rt, 24 h; (99%); (iv) 5% catalyst **7**, toluene, 50 °C, N_2, 48 h, complex mixture; (v) MCPBA (2.2 equiv), CH_2Cl_2, −5 °C, 48 h; (71%); (vi) 5% catalyst **7**, $CHCl_3$, rt, 24 h, then 45 °C, 24 h (95%); (vii) 10% [RuClH(CO)(PPh_3)$_3$], toluene, 105 °C, 24 h (84%); (viii) 5% catalyst **7**, toluene, 50 °C, 24 h, then further 5% catalyst **7**, 80 °C, 24 h, **23** (41%) and **22** (59%).

and to our knowledge these results are the first examples of high-yielding metathesis reactions between a phenolic vinyl ether and an enamine alkene.[19]

To enable facile deprotection of the nitrogen functional group, the Boc-protected precursor **12b** was also synthesized as described in Scheme 3. Application of the isomerization–RCM approach readily afforded the Boc-protected 3,4-dihydro-2*H*-1,4-benzoxazine compound **14b**.[20] Satisfyingly, in addition, both precursors **12a** and **12b** afforded the expected 8-membered benzo-fused oxazocine ring systems **15a**[21] and **15b** in acceptable yields of 69% and 70%, respectively, when treated with Grubbs' second generation catalyst **7**.

4. *N*-Substituted 5,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide and 2,5-dihydro-1,5-benzothiazepine 1,1-dioxide

RCM of substrates containing sulfur atoms has also seen a recent surge of interest.[22] However the application of RCM to synthesize benzo-fused *S*-containing heterocycles has seldom been done.[23] We thus decided to test whether we could synthesize the 8- and 6-membered benzo-fused ring systems containing the heteroatoms nitrogen and sulfur. Aminothiol **16** was thus monoalkylated with allyl bromide[24] and the amine subsequently protected with a tosyl group to afford compound **17** (Scheme 4). Furthermore, an allylation readily afforded compound **18**. Surprisingly, RCM on this substrate did not give the expected 8-membered benzothiazocine compound **19** and attempted isomerization of the same substrate was also unsuccessful.[14c]

Substrate **18** was thus oxidized to the corresponding sulfone **20** and this time the RCM successfully afforded the desired product **21**[25] in good yield although the reaction was quite sluggish (Scheme 4). The phenomenon of the oxidized substrate more readily engaging in metathesis has been observed before, in particular by Hanson and co-workers.[23b] Finally, we attempted to apply the sequential isomerization–RCM strategy on compound **20** and were rather surprised to isolate compound **22** in which only the *N*-allyl group had been isomerized. Kuźnik et al.[14c] have shown that allyl sulfones can be isomerized to the thermodynamically more stable compounds but in our hands we were unable to obtain the bis-isomerized product. Subsequently, when compound **22** was treated with Grubbs' catalyst **7**, the 7-membered 1,5-benzothiazepine **23** was obtained although the reaction was particularly slow.[26,27]

We have thus shown that the versatile RCM reaction, with the Grubbs' second-generation catalyst **7**, can be applied to the synthesis of a number of bicyclic compounds, namely *N*,*N*-, *N*,*O*- and *N*,*S*-8-membered benzo-fused heterocycles. In addition the application of a sequential isomerization–RCM strategy afforded the respective *N*-,*O*-6-membered benzo-fused bicyclic compounds in a novel manner although this strategy was not successful on the *N*-,*N*-substrates. Finally, a 7-membered benzothiazepine system was synthesized by a selective isomerization, followed by RCM. The extension of this work to the synthesis of other interesting systems is currently under investigation.

Acknowledgements

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University of the Witwatersrand (University and Science Faculty Research Councils). Professor C. B. de Koning is thanked for comments regarding the manuscript. Mr. R. Mampa and Mr. T. van der Merwe are also thanked for providing the NMR and MS spectroscopy services, respectively.

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11. 5,10-Bis-[(4-methylphenyl)sulfonyl)-5,6,9,10-tetrahydro-pyrido[2,3-*b*][1,4]diazocine **6b**: mp: 176–178 °C; Found: M^+: 469.11281; $C_{23}H_{23}N_3O_4S_2$ requires 469.11300; ν_{max} (thin film/cm^{-1}): 1595, 1569, 1377, 1344, 1159; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): 8.26 (dd, 1H, J = 4.5 and 1.5, ArH), 8.01 (dd, 1H, J = 8.1 and 1.5, ArH), 7.84 (d, 2H, J = 8.2, 2 × ArH), 7.74 (d, 2H, J = 8.2, 2 × ArH), 7.33-7.28 (m, 4H, 4 × ArH), 7.22 (dd, 1H, J = 8.1 and 4.5, ArH), 5.70–5.64 (m, 1H, –*H*C═CH), 5.57–5.53 (m, 1H, –HC═C*H*), 4.53 (d, 2H, J = 7.3, CH_2–CH), 3.99 (d, 2H, J = 4.8, CH_2–CH), 2.42 (s, 3H, ArCH_3), 2.41 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ 147.8 (ArC), 146.7 (C-2), 144.2 (ArC), 143.7 (ArC), 138.8 (ArCH), 136.1 (ArC), 134.9 (ArC), 132.8 (ArC), 129.9 (ArCH), 129.8 (2 × ArCH), 129.2 (2 × ArCH), 129.0 (2 × ArCH), 128.1 (2 × ArCH), 126.9 (C═C), 122.9 (C═C), 48.0 (CH_2), 46.1 (CH_2), 21.6 (ArCH_3), 21.5 (ArCH_3); *m*/*z* (EI): 469.1 (M^+, 18%), 315.1 (20), 314.1 (78), 250.1 (100), 159 (98), 91.1 (57), 69.1 (34), 41.1 (20).
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13. Crystallographic data for compound **6a**: $C_{24}H_{24}N_2O_4S_2$, crystal size 0.5 × 0.5 × 0.5 mm^3, crystal system monoclinic, space group $P2_1/c$, Z = 4, unit cell dimensions: a = 13.036(5) Å, b = 11.033(5) Å, c = 16.489(5) Å, β = 106.115(5)°, V = 2278.4(15) Å^3, D_x = 1.366 mg/m^3, collection temperature 293(2) K; θ_{max} = 28.29°; 15,395 reflections collected with 5604 independent reflections (R_{int} = 0.0201); 291 parameters; maximum residual electron density 0.299 and −0.286 e Å^{-3}; final R indices: R_1 = 0.0434, wR_2 = 0.1134. CCDC-249593 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
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17. 4-[(4-Methylphenyl)sulfonyl]-4*H*-1,4-benzoxazine **14a**: mp: 101–103 °C; Found: M^+, 287.0633; $C_{15}H_{13}NO_3S$ requires 287.0616; ν_{max} (thin film/cm^{-1}): 1666, 1599, 1357, 1171; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): 7.63–7.60 (m, 1H, ArH), 7.43 (d, 2H, J = 8.2, 2 × ArH), 7.19 (d, 2H, J = 8.2, 2 × ArH), 7.07–7.03 (m, 2H, 2 × ArH), 6.61–6.57 (m, 1H, ArH), 6.18 (d, 1H, J = 4.1, –*H*C═CH), 5.97 (d, 1H, J = 4.1, –HC═C*H*), 2.39 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ 149.2 (ArC), 144.4 (ArC), 137.3 (ArCH), 132.3 (ArC), 129.3 (2 × ArCH), 128.0 (2 × ArCH), 127.8 (ArCH), 125.3 (ArC), 125.2 (ArCH), 124.3 (ArCH), 116.4 (OCH), 109.9 (NCH), 21.6 (ArCH_3); *m*/*z* (EI): 287.1 (M^+, 13%), 132.1 (100), 91.1 (8), 77 (21), 65 (7), 51 (7).
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25. 6-[(4-Methylphenyl)sulfonyl]-5,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide **21**: mp: >230 °C; Found: M^+, 363.0626; $C_{17}H_{17}NO_4S_2$ requires 363.0599; ν_{max} (thin film/cm^{-1}): 1521, 1313, 1142; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si, assignments with the same superscript may be interchanged): 8.10–8.07 (m, 1H, ArH), 7.90 (d, 2H, $J = 8.2$, 2 × ArH), 7.60–7.57 (m, 2H, 2 × ArH), 7.40 (d, 2H, $J = 8.2$, 2 × ArH), 7.18–7.15 (m, 1H, ArH), 5.83–5.74 (m, 1H, –*H*C═CH), 5.65–5.59 (m, 1H, –HC═C*H*), 4.72–4.48 (br m, 2H, CH_2–CH), 3.88–3.60 (br m, 2H, CH_2–CH), 2.48 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ 145.0 (ArC), 139.8 (ArC), 135.2 (ArC), 134.8 (ArC), 134.2 (ArCH), 131.7 (ArCH), 130.3 (ArCH), 130.1 (2 × ArCH), 128.8 (2 × ArCH), 128.3 (ArCH)[a], 127.8 (C═C)[a], 122.5 (C═C), 56.0 (CH_2), 50.3 (CH_2), 21.7 ($ArCH_3$); *m*/*z* (EI): 363 (M^+, 9%), 256 (35), 243 (15), 220 (22), 185 (16), 129 (31), 83 (40), 69 (88), 41 (100).
26. 5-[(4-Methylphenyl)sulfonyl]-2,5-dihydro-1,5-benzothiazepine 1,1-dioxide **23**: mp: 191–192 °C with decomposition; Found: M^+, 349.0446; $C_{16}H_{15}NO_4S_2$ requires 349.0442; ν_{max} (thin film/cm^{-1}): 1663, 1598, 1328, 1170; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): 8.01 (d, 1H, $J = 7.8$, ArH), 7.86 (d, 1H, $J = 8.0$, ArH), 7.75–7.70 (m, 1H, ArH), 7.64 (d, 2H, $J = 8.2$, 2 × ArH), 7.56–7.51 (m, 1H, ArH), 7.26 (d, 2H, $J = 8.2$, 2 × ArH), 6.95 (d, 1H, $J = 9.8$, N–*H* C═CH), 5.03–4.97 (m, 1H, –HC═C*H*CH_2), 3.70 (dd, 2H, $J = 4.7$ and 1.4, –HC═CHCH_2), 2.41 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ 144.7 (ArC), 136.5 (ArC), 135.5 (ArC), 134.8 (ArC), 134.4 (ArCH), 131.3 (ArCH), 129.3 (2 × ArCH), 128.5 (4 × ArCH), 127.8 (NCH), 104.1 (HC=*C*HCH$_2$), 53.6 (CH_2), 21.7 ($ArCH_3$); *m*/*z* (EI): 349 (M^+, 6%), 285 (38), 221 (23), 194 (18), 155 (5), 130 (100), 91 (30), 65 (11), 39 (8).
27. For reviews on 1,5-benzothiazepines see: (a) Levai, A. *J. Heterocycl. Chem.* **2000**, *37*, 199–214; (b) Chimirri, A.; Gitto, R.; Grasso, S.; Monforte, A. M.; Zappala, M. *Adv. Heterocycl. Chem.* **1995**, *63*, 62–101.