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Formation of an unexpected rearrangement product using Grubbs' second generation catalyst: 2-allyl-3,4-dihydro-2*H*-1,4-benzothiazines from diene precursors

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ABSTRACT

Application of sub-stoichiometric amounts of Grubbs' second generation catalyst to the substrate *N*-allyl-*N*-[2-(allylsulfanyl)phenyl]-4-methylbenzenesulfonamide afforded the ring-closed compound 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-2*H*-1,6-benzothiazocine, as well as the unexpected 2-allyl-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-1,4-benzothiazine. Use of similar conditions on an analogous sulfoxide resulted in the expected product, 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-2*H*-1,6-benzothiazocine 1-oxide, indicating that the sulfide was playing a key role in this novel transformation. Furthermore, the use of *N*-allyl-4-methyl-*N*-{2-[(2-methyl-2-propenyl)sulfanyl]phenyl}-benzenesulfonamide in the same reaction gave 2-(2-methyl-2-propenyl)-3,4-dihydro-2*H*-1,4-benzothiazine.

Ring-closing metathesis (RCM) has become an established methodology for the construction of medium-sized ring systems containing various heteroatoms.[1] Due to the extensive use of metathesis catalysts, exemplified by the Grubbs' first and second generation catalysts, researchers occasionally report unforeseen results from the use of RCM. These unexpected results represent a wide selection of synthetic transformations including pre- and post-metathetic isomerizations and oxidative rearrangements, which have been reviewed by Alcaide and Almendros.[2a,b] Of interest is that in terms of the amount of ruthenium carbene required, examples of catalytic and stoichiometric reactions have been recorded. In addition, a number of these ruthenium-mediated side reactions have found synthetic application.[2c,d]

In terms of the heteroatoms incorporated into ring systems utilizing the RCM approach, the formation of sulfur-containing heterocycles has been less described than with atoms such as nitrogen or oxygen.[3] This may, in part, be due to the coordination of sulfur with the metal carbene center, sometimes resulting in complex reaction mixtures or in no reactions at all.

We have been interested in exploring the synthesis of benzo-fused heterocycles,[4] including six- and seven-membered heterocycles containing sulfur in various oxidation states.[5] For example, we synthesized 1,4-benzoxathiin (**3a**) and 1,4-benzodithiin (**3b**) by way of an isomerization-RCM strategy as depicted in Scheme 1.[5b]

In this Letter, we report how the application of larger than usual amounts of the Grubbs' second generation catalyst (**4**)[6] to *N*-allyl-*N*-[2-(allylsulfanyl)phenyl]-4-methylbenzenesulfonamide (**1c**) gave the unexpected product 2-allyl-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-1,4-benzothiazine (**5**) (Scheme 2) as one of the two major products.[7]

During research into the application of metathesis to sulfur-containing compounds the allyl sulfides **1a–c** were treated with the Grubbs' second generation catalyst **4** (Scheme 3). Unfortunately, when applying the RCM reactions on compounds **1a** and **1b** in an attempt to obtain the benzannulated heterocycles **6a** and **6b**, respectively, no products were obtained. In fact, from TLC analysis, it appeared that the substrates were transformed directly into polymeric material which we were unable to characterize. The same reaction performed on diene **1c** gave rise to a fairly complex mixture of products.

After evaluation of the crude ^{1}H NMR spectrum of the latter experiment involving **1c**, in which evidence existed supporting the existence of products other than the starting material, it was decided to repeat this particular reaction with a larger quantity of catalyst to investigate the mixture of products formed.

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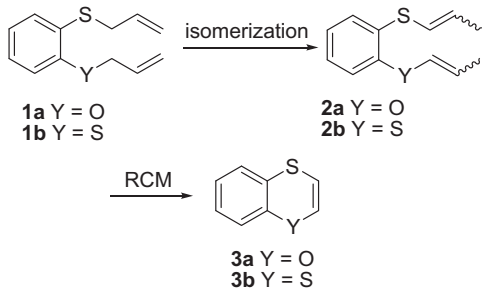
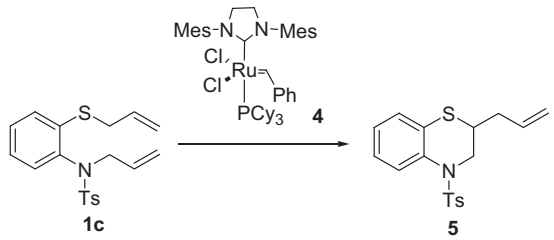
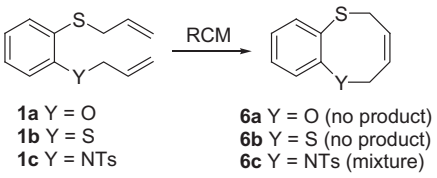


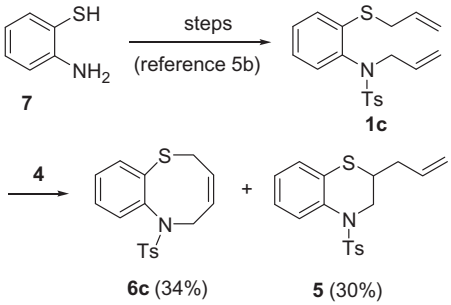
Scheme 1. Formation of 1,4-benzodithiin and 1,4-benzoxathiin as described in Ref. 5b.



Scheme 2. Formation of allyl-substituted benzo[1,4]thiazines.



Scheme 3. Conditions for the attempted RCM to afford **6a,b**: catalyst **4** (5–15 mol %), $CHCl_3$, see Ref. 5c for a description of the attempted synthesis of **6c**.



Scheme 4. Reagents and conditions: catalyst **4** (5 × 10% over 24 h = 50 mol %), $ClCH_2CH_2Cl$, N_2, 65–80 °C, 24 h.

Interestingly, the addition of sub-stoichiometric amounts of ruthenium carbene **4** (50 mol % applied in several portions during the course of the reaction) to substrate **1c** again gave rise to a mixture of products from which two compounds were isolated by careful column chromatography (Scheme 4).[8] The first product was the expected dihydro-2*H*-1,6-benzothiazocine **6c** (34%),[9] while the other was determined to be allyl-substituted benzo[1,4]thiazine **5**[9] in an approximately equal yield of 30%. Due to its unusual features the structure of compound **5** was unambiguously proved by a single crystal X-ray study (Fig. 1).[9] Of interest is that the substituted benzo[1,4]thiazine scaffold has elicited much interest in medicinal chemistry circles over the past decade,[10] making the development of potential new approaches to this substrate a worthwhile venture.

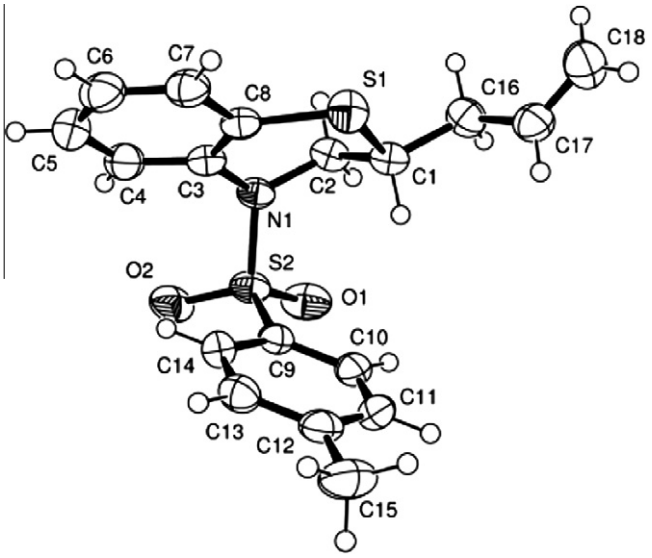
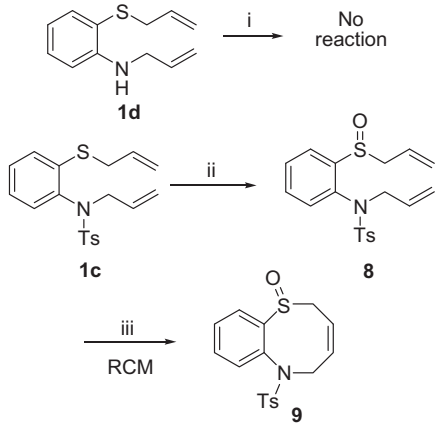
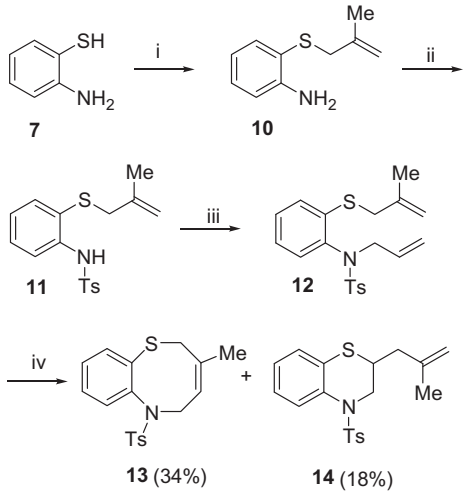


Figure 1. Single crystal X-ray structure for compound **5** (ORTEP diagram drawn at 50% probability level).

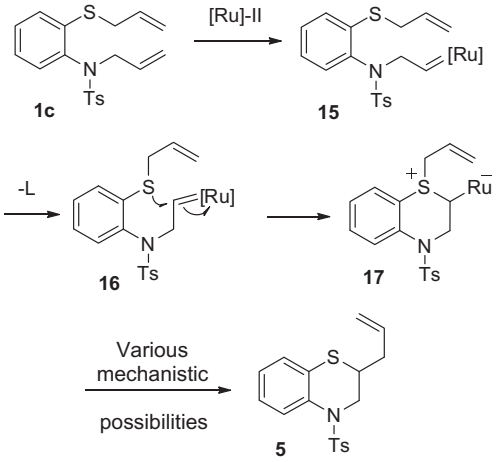


Scheme 5. Reagents and conditions: (i) catalyst **4** (20 mol %), 65–80 °C, 24 h (no product observed); (ii) *m*CPBA (1.1 mol equiv), 0 °C to rt, CH_2Cl_2, N_2, 18 h (92%); (iii) catalyst **4** (10 mol %), CH_2Cl_2, N_2, reflux, 20 h (95%).

Having already determined that this interesting reaction was not occurring when 1-(allyloxy)-2-(allylthio)benzene (**1a**) (Y=O) or 1,2-bis(allylthio)benzene (**1b**) (Y=S) (Scheme 2) was used as starting material, it was decided to probe a number of factors involved in the reaction. Firstly, reactions at lower temperature (−5 °C, rt and 40 °C) indicated that a higher temperature was required. In our hands, keeping the temperature in the range of 65–80 °C gave the best results. Secondly, we found it necessary to add larger than catalytic amounts of the Grubbs' second generation carbene (typically 50%) as at lower catalyst concentrations, while the product spots were evident on TLC, only very low yields of the products were obtained on work-up followed by chromatography. It was also established that the tosyl group was important, as substrate **1d** did not give the desired rearranged product (under the conditions employed it also did not give the ring-closed product) (Scheme 5). To probe whether the oxidation state of the sulfur atom was important, oxidation of **1c** to the sulfoxide **8** provided a product which readily gave the benzannulated heterocycle **9**, even under fairly mild conditions of dichloromethane at reflux. In addition, we had previously demonstrated that the sulfone version of this compound afforded the 8-membered 5,6-dihydro-2*H*-1,



Scheme 6. Reagents and conditions: (i) 3-bromo-2-methylprop-1-ene, NaOH, MeOH, 18 h (84%); (ii) TsCl, pyridine, CH_2Cl_2, 0 °C to rt, N_2, 18 h (quant.); (iii) allyl bromide, K_2CO_3, acetone, rt, 24 h (94%); (iv) catalyst **4** (4 × 10 and 2 × 5 mol %), $ClCH_2CH_2Cl$, N_2, 65–80 °C, 24 h.



Scheme 7. A possible mechanism for the formation of compound **5**.

6-benzothiazocine 1,1-dioxide in high yield under mild conditions (Scheme 5).[5c] This set of results indicated strongly that the sulfide was crucial to afford the rearrangement product **5**.

We decided to further investigate this intriguing result with the synthesis of substrate **12**, the difference being that this time the *S*-allyl group bears a 2′-methyl group. To this end, 2-aminothiophenol (**7**) was alkylated with 3-bromo-2-methylprop-1-ene to afford **10** in good yield. Tosylation and allylation of the aniline amino group then gave the substituted bis-allyl compound **12**. Application of the Grubbs' second generation catalyst (**4**) (50 mol %) afforded the substituted benzothiazine **14**[11] in 18% yield, along with the expected eight-membered dihydro-2*H*-1,6-benzothiazocine **13**,[12] presumably obtained by way of a normal metathetic cascade (Scheme 6).

The use of sub-stoichiometric amounts of Grubbs' catalyst **4** was a serious problem regarding the applicability of this methodology. We thus attempted to stabilize any important organometallic species with a number of phosphine ligands as an additive, but unfortunately to no avail. It should be noted that during the course of the reactions the color of the mixtures became progressively darker with time, a possible indication that insoluble ruthenium 'black' was being precipitated.

In terms of a postulated mechanism, it seems reasonable that compound **1c** is converted into the ylide **17** by the sulfur atom trapping the ruthenium carbene via an intramolecular attack (**1c**→**15**→**16**, Scheme 7). This would also account for the loss of the methylene fragment observed in the product **5**. There are then various options resulting in the final product. It was first considered possible that the rearrangement of **1c** into **5** occurs by way of a [2,3]-sigmatropic rearrangement.[13] In addition, it should be mentioned that a [1,2]-carbon shift (a Stevens rearrangement) is also possible.[14] The involvement of a ruthenium-mediated π-allyl species with a subsequent reductive elimination to give **5** could also be conceivable.[14a] Finally, a novel pericyclic reaction leading to the product can at this stage also not be ruled out. In view of the importance of allyl-transfer reactions in organic synthesis it is also envisaged that the unexpected reaction observed could lead to the development of novel C-allylation reactions.[15]

Conclusion

In conclusion, we have disclosed an unusual rearrangement product obtained when using the Grubbs' second generation carbene (**4**) on *N*-allyl-*N*-[2-(allylthio)phenyl]-4-methylbenzenesulfonamide (**1c**) and the related compound **12**. Despite the problem that the utilization of non-catalytic amounts of **4** poses, it is envisaged that this interesting rearrangement, which results in the potentially useful allyl-substituted benzo[1,4]thiazine **5** framework, will receive further synthetic attention. We intend to synthesize other substrates to see if the mechanism of this novel transformation can be elucidated, with a secondary aim of developing a catalytic version of this reaction.

Acknowledgments

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7. Experimental work performed by GLM (PhD) and DBY (postdoctoral fellow); crystallography by Dr M.A. Fernandes.

8. *Procedure giving rise to compounds **5** and **6c** with Grubbs' second generation catalyst **4***. Catalyst 4 (10 mol %) was added to *N*-allyl-*N*-[2-(allylthio)phenyl]-4-methylbenzenesulfonamide (**1c**) (0.096 g, 0.27 mmol) dissolved in 1,2-dichloroethane (25 mL) under N_2. The reaction was then stirred at 65–80 °C for 24 h with further portions of the catalyst being added until complete consumption of starting material was observed by TLC (another 40 mol % in 10 mol % portions). The reaction mixture was then filtered through a pad of Celite and silica gel (1:1) and the solvent removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (5–20% EtOAc/hexane) to afford compounds **5** (0.028 g, 30%) as white solid prisms (mp: 120–123 °C) and **6c** (0.031 g, 34%) as yellow solid cubic prisms (mp: 170–175 °C).
9. *Allyl-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2H-1,4-benzothiazine* (**5**). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.67–7.62 (1H, m), 7.48 (2H, d, J 8.3 Hz), 7.21 (2H, d, J 8.3 Hz), 7.14–6.95 (3H, m), 5.77–5.63 (1H, m), 5.22–5.00 (2H, m), 4.55 (1H, dd, J 14.3, 3.8 Hz,), 3.28–3.12 (1H, m), 3.06–2.98 (1H, m), 2.40 (3H, s), 2.39–2.13 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.9, 137.3, 134.1, 132.9, 129.7, 128.7, 127.2, 127.1, 126.5, 126.3, 124.5, 118.6, 49.8, 38.9, 37.9, 21.6; *m*/*z* (EI): 345 (M+, 76%), 190 (96), 148 (100), 136 (36), 109 (25), 91 (33), 65 (26), 55 (25); HRMS calculated for $C_{18}H_{19}NO_2S_2$ 345.0857, found 345.0837. Crystallized from EtOAc–hexane, formula: $C_{18}H_{19}NO_2S_2$, M = 345.46, colour of crystal: colourless, needle, crystal size = 0.46 0.31 0.08 mm^3, a = 14.0109(19) Å, b = 13.1138(18) Å, c = 9.3095(12) Å, β = 94.714(2)° V = 1704.7(4) Å^3, calc = 1.346 mg/m^3, μ = 0.321 mm^{-1}, F(000) = 728, Z = 4, monoclinic, space group P2(1)/c, T = 153(2) K, 9737 reflections collected, 3337 [R(int) = 0.0311] independent reflections, θ_{max} 26.00° 209 refined parameters, maximum residual electron density 0.741 and −0.499 e.Å^{-3}, R_1 = 0.0525, wR_2 = 0.1114. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-819331; 6-[(4-Methylphenyl)sulfonyl]-5,6-dihydro-2*H*-1,6-benzothiazocine (**6c**). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.69 (2H, d, *J* 8.1 Hz), 7.36–7.31 (3H, m), 7.23–7.18 (1H, m), 7.11–7.06 (1H, m), 6.74 (1H, d, *J* 7.8 Hz), 5.72–5.63 (1H, m), 5.48–5.40 (1H, m), 4.54–3.71 (4H, br m), 2.46 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.8, 138.3, 138.0, 136.2, 131.4, 129.6, 129.1, 128.9, 128.5, 127.9, 126.7, 125.8, 49.4, 29.8, 21.6; *m*/*z* (EI): 332 (M$^+$+1, 100%), 282 (10), 177 (15); HRMS calculated for $C_{17}H_{18}NO_2S_2$ (M+H)$^+$ 332.0773, found 332.0774.
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11. *4-[(4-Methylphenyl)sulfonyl]-2-(2-methyl-2-propenyl)-3,4-dihydro-2H-1,4-benzothiazine* (**14**). ^{1}H NMR (300 MHz, CDCl3): δ (ppm) 7.66–7.52 (1H, m), 7.41 (2H, d, *J* 8.1 Hz), 7.25–7.07 (2H, m), 7.04–6.95 (3H, m), 4.78 (1H, s), 4.66 (1H, s), 4.47 (1H, dd, *J* 14.4, 3.6 Hz), 3.24–3.11 (1H, m), 3.00–2.80 (1H, m), 2.32 (3H, s), 2.20 (1H, dd, *J* 14.2, 6.5 Hz), 2.14–1.96 (1H, m), 1.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 144.0, 140.2, 137.4, 133.9, 129.8, 128.8, 127.5, 127.1, 126.4, 126.3, 124.4, 113.8, 50.1, 42.1, 36.8, 22.0, 21.6; *m*/*z* (EI): 360 (M$^+$+1, 50%); HRMS calculated for $C_{19}H_{22}NO_2S_2$ (M+H)$^+$ 360.1087, found 360.1087.
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