Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 659–662

Tetrahedron Letters

Synthesis of dienynes from alkenes and diynes using ruthenium-mediated ring-closing metathesis

Willem A. L. van Otterlo,* E. Lindani Ngidi, Charles B. de Koning and Manuel A. Fernandes

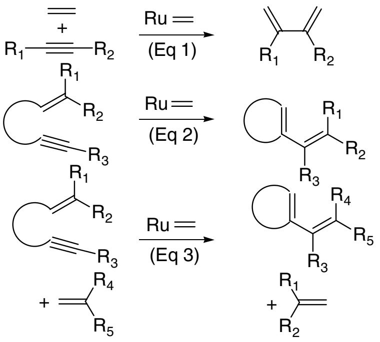
Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050 Johannesburg, South Africa

Received 22 October 2003; accepted 14 November 2003

Abstract—This communication describes a novel ruthenium-mediated transformation, which converts molecules containing alkenes and conjugated diynes such as 1-allyl-2-{[6-(2-allylphenoxy)-2,4-hexadiynyl]oxy}benzene into dienynes such as 3-[2-(2,5-dihydro-1-benzoxepin-3-yl)-1-methylene-2-propenyl]-2,5-dihydro-1-benzoxepine instead of the expected product 3-[2-(2,5-dihydro-1-benzoxepin-3-yl)ethynyl]-2,5-dihydro-1-benzoxepine.

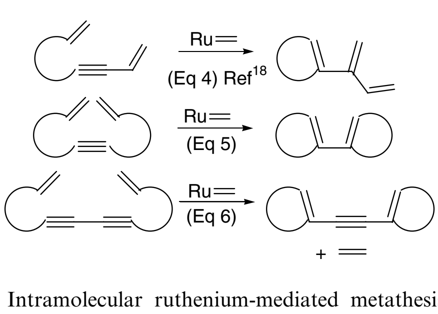
© 2003 Elsevier Ltd. All rights reserved.

Transition-metal mediated alkene–alkene metathesis has grown exponentially in the last decade.[1–3] Ene–yne metathesis[4,5] on the other hand is still fairly novel and this arena of metathesis is steadily finding applications in organic synthesis. The latter form of metathesis entails the metal-mediated interaction of an alkyne with 1 or 2 equiv of alkene, generally resulting in the formation of a conjugated diene in the product skeleton. The products formed can be derived from inter-[6] (Eq. 1), intra-[7–9] (Eq. 2) or mixed intra- and intermolecular[10] reactions (Eq. 3) as shown in Scheme 1.



Scheme 1. Inter-, intra- and mixed inter- and intramolecular ene–yne ruthenium-mediated metathesis reactions.

Part of our ongoing research programme involves the synthesis of benzo-fused bicyclic molecules.[11–14] Our approach has recently included the application of ruthenium-mediated ring-closing metathesis (RCM) for the synthesis of these molecules.[15–17] Recently Chang and co-workers have reported that the intramolecular RCM of alkenyl enynes afforded triene systems in moderate yields as depicted by Eq. 4 in Scheme 2.[18] This and the fact that the intramolecular metathesis of two terminal alkene functional groups with an yne system (Eq. 5) has been described before by Grubbs[19] and others[8] has prompted us to disclose our results in this area. In this communication we thus wish to describe a new result from the intramolecular metathesis reaction between two terminal alkenes and a conjugated diyne system (Eq. 6) using catalyst **1**.[20] This reaction results in the formation of a novel bicyclic system containing a formally conjugated *dienyne* system.



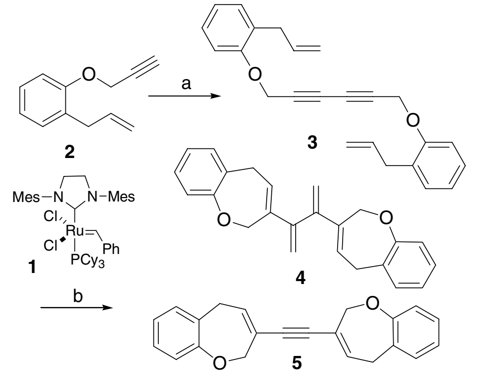
Scheme 2. Intramolecular ruthenium-mediated metathesis reactions with alkenes and alkynes.

Keywords: Ruthenium; Metathesis; Diynes; Dienynes.

* Corresponding author. Tel.: +27-11-717-6707; fax: +27-11-717-6749; e-mail: willem@aurum.chem.wits.ac.za

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.063

In the initial stages of this work the first precursor for this reaction, substrate **3**, was synthesized by the copper-mediated acetylenic coupling of propargyl ether **2** (Scheme 3).[21] Reaction of **3** under commonly used metathesis conditions did not afford the expected product **4** but rather gave us the symmetrical acetylene **5**.[22] This intriguing result meant that the diene–diyne system of the starting material had surprisingly been converted into a dienyne system **5** rather than the tetraene system **4** as would be expected from comparison with the work of Chang and co-workers.[18] The overall reaction process for this conversion necessitates the expulsion of ethylene gas. The mechanisms proposed for metal-mediated metathetic reactions are often described as being complex, with the ultimate product produced being thermodynamically favoured. The loss of ethylene should therefore entropically promote the formation of product **5** over **4**.[23]



Scheme 3. Reagents and conditions: (a) CuCl, TMEDA, O_2, acetone, reflux, 53%; (b) **1** (6 mol%×2), toluene, 80 °C, ethylene atmosphere (1 atm), **4**, 0%, **5**, 54%.

The structure of the product formed by this novel ruthenium-catalyzed reaction was confirmed by a single crystal X-ray determination (Fig. 1).[24,25] We believe that this reaction constitutes the first example of a metathesis reaction, which leads to the overall conversion of alkenes and conjugated diynes into a *diene–yne* system. Examples of the synthesis of conjugated yne–diene systems have been reported[26] and a reaction forming the same type of diene–yne product from two conjugated diyne substrates has also been described, albeit by a light-induced mechanism.[27]

Initial optimization experiments utilizing substrate **3** led us to conclude that dilute conditions and shorter reaction times promoted the formation of product in higher yields. In particular, the use of an ethylene atmosphere (1 atm) was beneficial. This phenomenon has also been observed by other workers doing enyne metathesis reactions.[4] The reaction was then tested on several other substrates and the results are listed in Scheme 4 below. We found that acetylene-fused five- and six-membered heterocyclic rings with nitrogen or oxygen as the heteroatom **7a–d** could be accessed in variable yields from **6a–d** using our methodology.

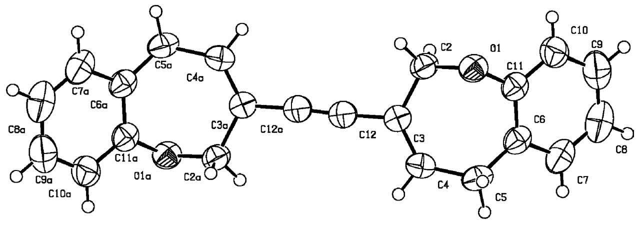
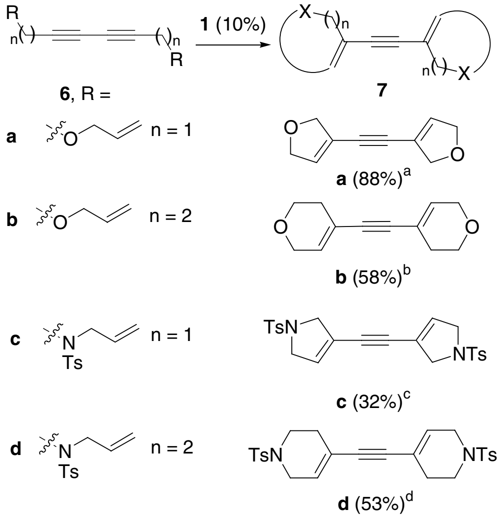


Figure 1. X-ray crystal structure of compound **5**.



Scheme 4. Reagents and conditions: All compounds were synthesized according to the general procedure[22] with the following variations [a]5 h, 0.013 M; [b]15 h, 0.011 M; [c]2×15 h, 0.010 M, 2×6 mol% **1**, N_2 (ethylene gas gave a complex mixture of products); [d]16 h, 0.010 M.

Unfortunately attempts to cyclize substrates **6e**, **6f** and **6g** under the optimized conditions were unsuccessful (Fig. 2). Reactions using these substrates either resulted in complex product mixtures or returned the starting material. We are currently investigating this phenomenon in additional studies.

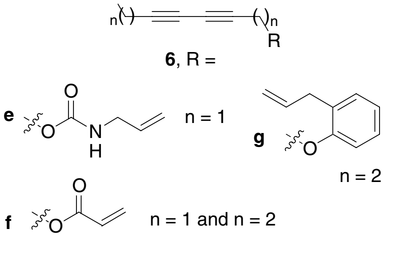
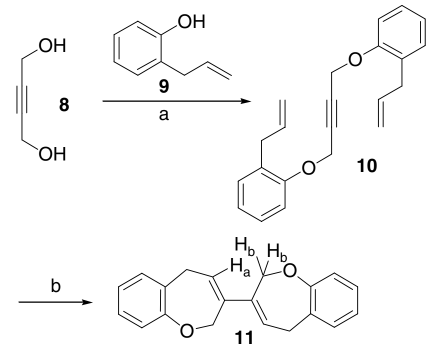


Figure 2. Unsuccessful substrates.

Finally we also tested the intramolecular ruthenium-mediated metathesis (of the type shown in Eq. 4) on substrate **10**, containing only one alkyne, which was synthesized from 2-butyne-1,4-diol **8** and commercially available 2-allylphenol **9** using Mitsunobu methodology (Scheme 5). Standard metathesis conditions afforded the expected bis(benzoxepine) **11** in good yield.



Scheme 5. Reagents and conditions: (a) DEAD, PPh_3, THF, rt, 16 h, 95%; (b) **1** (10%), toluene, 60 °C, 71%.

A single crystal X-ray structure determination confirmed our proposed structure (Fig. 3).[25,28] The central core of the molecule is virtually planar as the alkene proton H_a is positioned between the two hydrogen atoms H_b adjacent to the oxygen atom on the opposing benzoxepine. This structural feature suggests that the monocyclized intermediate is preorganized to minimize steric interaction and that the second metathesis then traps the molecule in the preferred orientation as shown in the crystal structure.

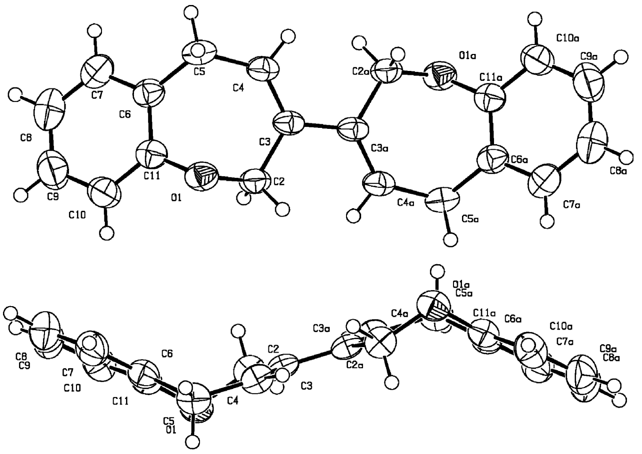


Figure 3. X-ray crystal structure of compound **11**.

In conclusion, we have discovered a novel transformation, which converts conjugated diynes into diene–yne systems. We plan to extend this research by investigating the scope of this reaction and hope to synthesize a range of interesting products with potential applications in pharmaceutical and materials chemistry.

Acknowledgements

This work was supported by the National Research Foundation (NRF, GUN 2053652), Pretoria, and the University of the Witwatersrand (University Research Council). We also thank the Mellon Postgraduate Mentoring Programme (sponsored by the Andrew W. Mellon Foundation) for generous funding. Prof. J. P. Michael is thanked for many helpful discussions.

References and notes

1. Grubbs, R.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
2. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.
3. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
4. Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18.
5. Mori, M. Enyne metathesis. In *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998; pp 133–154.
6. Some recent examples (a) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224–226; (b) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235–2238; (c) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793–1796; (d) Kotha, S.; Halder, S.; Brahmachary, E. *Tetrahedron* **2002**, *58*, 9203–9208; (e) Lee, H-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855–1858; (f) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819–3822.
7. Recent ene–yne examples (a) Dolhem, F.; Lièvre, C.; Demailly, G. *Eur. J. Org. Chem.* **2003**, 2336–2342; (b) Le Flohic, A.; Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* **2003**, 667–670; (c) Royer, F.; Vilain, C.; Elkaïm, L.; Grimaud, L. *Org. Lett.* **2003**, *5*, 2007–2009; (d) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582–9583; (e) Katritzky, A. R.; Nair, S. K.; Khokhlova, T.; Akhmedov, N. G. *J. Org. Chem.* **2003**, *68*, 5724–5727.
8. Recent diene–yne examples (a) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323–2325; (b) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2003**, *44*, 8047–8049; (c) Wu, C.-J.; Madhushaw, R. J.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 7889–7892; (d) Efskind, J.; Undheim, K. *Tetrahedron Lett.* **2003**, *44*, 2837–2839; (e) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417–2420.
9. Examples of a recent ene–yne ring-rearrangements/cross metathesis (a) Imhof, S.; Blechert, S. *Synlett* **2003**, 609–614, and metathesis cascades; (b) Banti, D.; North, M. *Tetrahedron Lett.* **2003**, *44*, 8157–8160; (c) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291–4298.
10. (a) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272–3276; (b) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439–3442.
11. de Koning, C. B.; Green, I. R.; Michael, J. P.; Oliveira, J. R. *Tetrahedron* **2001**, *57*, 9623–9634.
12. de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 799–811.
13. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787–797.
14. de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *Synlett* **2002**, 2065–2067.
15. van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311–313.
16. van Otterlo, W. A. L.; Ngidi, E. L.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 6483–6486.
17. van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859–1861.

18. Kang, B.; Kim, D.-H.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041–3043.
19. Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.
20. From the ongoing MSc of E. L. Ngidi.
21. Moreno–Mañas, M.; Pleixats, R.; Santamaria, A. *Synlett* **2001**, 1784–1786.
22. Grubbs catalyst **1** (0.017 g, 0.02 mmol, 6 mol%) was added to a solution of 1-allyl-2-{[6-(2-allylphenoxy)-2,4-hexadiynyl]-oxy}benzene **3** (0.12 g, 0.35 mmol) in degassed toluene (16 mL, 0.013 M), and the solution was heated at 80 °C for 15 h under an ethylene atmosphere (1 atm). A further portion of the catalyst (0.017 g, 0.02 mmol, 6 mol%) was added and the heating continued for another 15 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (5% ethyl acetate–hexane) to afford 3-[2-(2,5-dihydro-1-benzoxepin-3-yl)-1-methylene-2-propenyl]-2,5-dihydro-1-benzoxepine **5** (0.060 g, 0.19 mmol, 54%) as a light yellow crystalline material, recrystallized from methanol–hexane, mp = 122–125 °C. Found: M^+, 314.1309, $C_{22}H_{18}O_2$ requires 314.1307; ν_{max} ($CHCl_3$)/cm^{-1} 1585, 1492, 1458, 1210; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.53$ (4H, dt, $J = 5.8$ and 2.0 Hz, 2×$ArCH_2$), 4.50 (4H, dt, $J = 2.0$ and 2.0 Hz, 2×OCH_2), 6.24 (2H, tt, $J = 5.8$ and 2.0 Hz, 2×HC=), 7.00–7.09 (6H, m, ArH), 7.17–7.23 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.5$ ($ArCH_2$), 72.6 (OCH_2), 86.6 (C≡C), 121.2 (CH), 121.8 (C), 124.4 (CH), 128.2 (CH), 128.8 (CH), 133.2 (CH), 134.7 (C), 158.2 (C–O); HRMS: $m/z = 315$ (M^++H, 23%), 314 (M^+, 100), 313 (M^+−H, 11), 299 (14), 208 (12), 207 (19), 195 (15), 194 (13), 181 (13), 165 (19), 149 (26), 131 (12), 119 (10), 91 (21), 71 (12), 57 (17), 55 (11).
23. The relative stability of product **5** versus the cross-conjugated tetraene system **4** is presently being investigated by molecular modeling.
24. Crystal data for **5**: $C_{22}H_{18}O_2$, crystal size 0.30×0.30×0.16 mm^3, crystal system monoclinic, space group $P2_1/c$, $Z = 2$, unit cell dimensions: $a = 16.914(2)$ Å, $b = 6.3517(9)$ Å, $c = 7.9430(11)$ Å, $\beta = 97.814(3)°$, $V = 845.4(2)$ Å^3, $D_c = 1.235$ Mg/m^3, collection temperature 293(2) K; $\theta_{max} = 24.98$; 2356 reflections collected with 1325 independent reflections ($R_{int} = 0.0282$); 110 parameters; maximum residual electron density 0.154 and −0.101 eÅ^{-3}; final R indices: $R_1 = 0.0370$, $wR_2 = 0.0966$. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 222162. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-0-1223-336033 or email: deposit@ccdc.cam.ac.uk).
25. Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA), wavelength 0.71073 Å, data reduction was carried out using the program SAINT+[Bruker 1999, SAINT+.Version 6.02 (includes XPREP and SADABS). Bruker AXS Inc., Madison, Wisconsin, USA] and face indexed absorption corrections were made using the program XPREP, The crystal structure was solved by direct methods using SHELXTL. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using SHELXTL [Bruker 1999, *SHELXTL*. Version 5.1. (includes XS, XL, XP, XSHELL) Bruker AXS Inc., Madison, Wisconsin, USA.] and the data further processed using the program SADABS (Sheldrick, G. M. 1996, SADABS, University of Göttingen, Germany.] Hydrogen atoms were first located in the difference map and then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON (Spek, A.L. Acta Cryst. 1990, A46, C-34).
26. (a) Hartung, I. V.; Niess, B.; Haustedt, L. O.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3239–3242; (b) Zhao, Y.; Tykwinski, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 458–459; (c) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816–2818; (d) Katz, T. J.; Yang, G. X.-Q.; Rickman, B. H.; Iwashita, T. *J. Am. Chem. Soc.* **1993**, *115*, 2038–2039.
27. Kiji, J.; Konishi, H.; Okano, T.; Koyuhara, N.; Sakakibara, M. *Chem. Lett.* **1985**, 35–36.
28. Crystal data for **11**: $C_{20}H_{18}O_2$, crystal size 0.52×0.48×0.22 mm^3, crystal system monoclinic, space group $P2_1/c$, $Z = 2$, unit cell dimensions: $a = 15.216(3)$ Å, $b = 6.2751(13)$ Å, $c = 8.0930(17)$ Å, $\beta = 104.898(4)°$, $V = 746.7(3)$ Å^3, $D_c = 1.291$ Mg/m^3, collection temperature 293(2) K; $\theta_{max} = 28.30$; 4971 reflections collected with 1857 independent reflections ($R_{int} = 0.0239$); 101 parameters; maximum residual electron density 0.230 and −0.141 eÅ^{-3}; final R indices: $R_1 = 0.0434$, $wR_2 = 0.1230$. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 222163. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-0-1223-336033 or email: deposit@ccdc.cam.ac.uk).