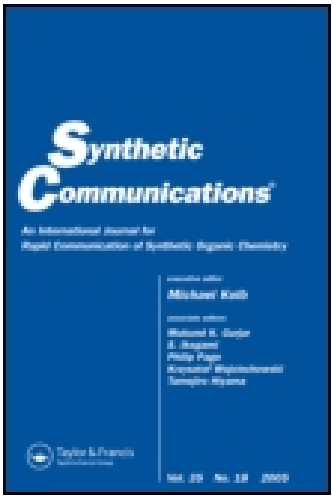

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Unexpected Dehydrogenation Products in the Furan Series Arising from Ruthenium-Catalyzed 4-Oxo-1,6-enyne Metathesis

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Unexpected Dehydrogenation Products in the Furan Series Arising from Ruthenium-Catalyzed 4-Oxo-1,6-enyne Metathesis

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Abstract: Metathesis of 4-oxo-1,6-enynes afforded the usual dihydrofuran products accompanied for the first time by unexpected side products identified as the corresponding furans. It probably arose from ruthenium-catalyzed dehydrogenation of dihydrofurans in the metathesis reaction mixture.

Keywords: Aromatization, dehydrogenation, enyne metathesis, furan

INTRODUCTION

Ring-closing enyne metathesis (RCEYM) is an intramolecular bond reorganization of an alkene and an alkyne (**I**) to produce a cyclic 1,3-diene **II** (Scheme 1).[1] This reaction catalyzed by Grubbs' ruthenium complexes **1** and **2** has been applied to the short synthesis of unsaturated heterocycles, especially azacyclic[2] and oxacyclic dienes,[3] which are useful synthons in the synthesis of more complex heterocycles.[1,4] Herein, we report an unexpected dehydrogenation product arising from our attempts to prepare oxacyclic dienes of type **II** (X = O).

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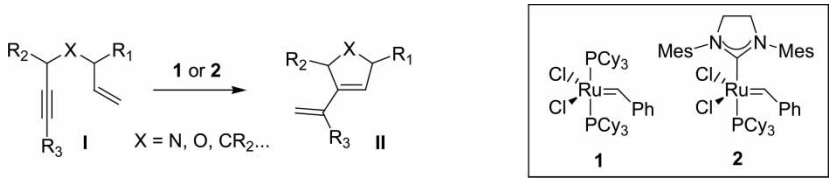


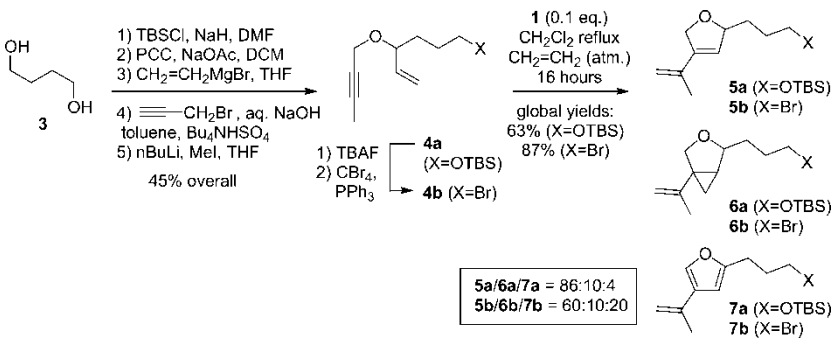
Scheme 1. The general ring-closing enyne metathesis reaction and the metathesis catalysts **1** and **2** (framed).

RESULTS AND DISCUSSION

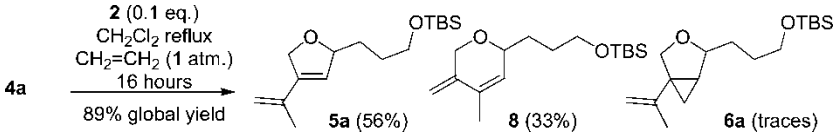
In the course of our work toward the synthesis of natural products, we envisaged to use RCEYM to form dihydrofuran building blocks from 4-oxo-1,6-enynes in the presence of the first generation Grubbs' catalyst (**1**). Enyne **4a** (Scheme 2) was synthesized in five sequential steps and 45% overall yield from butan-1,4-diol (**3**),[5,6] and was also brominated into **4b** (PPh_3/CBr_4) in 78% yield after deprotection of the hydroxyl.

The metathesis step proceeded in the presence of catalyst **1** in refluxing dichloromethane and under an atmosphere of ethylene, affording the dihydrofurans **5a**, **b** and side products **6a**, **b** and **7a**, **b** (63% and 87% global yields in the *O*-silylated and brominated series, respectively). Neither the *O*-silylated nor the brominated products **5a**, **b**; **6a**, **b**; and **7a**, **b** were separable by chromatography at this stage. It is worthy of note that the formation of the side products, especially **7**, proved to be uncertain and appeared to us unpredictable, so we tried to investigate it.

RCEYM of compound **4a** was also attempted in the presence of the second generation Grubbs' catalyst **2** (Scheme 3). As expected and according to the results obtained by Mori et al.,[4b] two major products were isolated: the dihydrofuran **5a** (56% yield) and the isomeric *exo*-methylene dihydropyran **8**



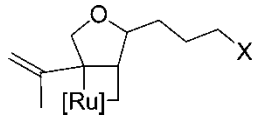
Scheme 2. Synthesis of dihydrofuran derivatives **5a**, **b** from enynes **4a**, **b** and side products (**6a**, **b**; **7a**, **b**) observed during metathesis.



Scheme 3. RCEYM of enyne **4a** with catalyst **2**.

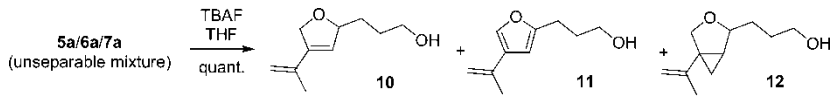
(33%). Moreover, traces of the cyclopropane derivative **6a** were also observed by mass spectrometry, but no dehydrogenated product **7a** in this case.

In all these metathesis reactions, cyclopropane side products **6a**, **b** were only present in about 10% of the mixture (quantity limited by the amount of catalyst) and were mainly observed by mass spectrometry, showing an extra methylene group, and by NMR spectroscopy, showing residual peaks characteristic of the cyclopropane moiety in the high fields. Such products have already been described by Mori et al.[2] in the pyrrolidine series and could be formed by reductive elimination of the ruthenium complex $RuCl_2(PCy_3)_2$ from the ruthenacyclobutane intermediate **9** occurring in the catalytic cycle. They were always observed in our experiments and the cyclopropane derivative **12** could be fully characterized after deprotection of **6a** (Scheme 4).



9, [Ru] = $RuCl_2(PCy_3)_2$

In the case of the reactions with the first generation Grubbs' catalyst (**1**), the other side products (**7a**, **b**) were surprisingly identified as furan derivatives by ^1H NMR, ^{13}C NMR, and mass spectrometry. As for compound **6a**, furan **7a** was characterized after deprotection of the silylated hydroxyl group of the product mixture from metathesis of enyne **4a** (Scheme 4). Indeed, subsequent separation by silica-gel chromatography gave the labile compound **10** (53%, overall yields from enyne **4a**) and the pure furan derivative **11** (4%), along with cyclopropane **12** (6%). It is important to mention that some furan-free samples of dihydrofuran **5a** yielded up to 34% of furan **11** after desilylation that was later attributed to residual contamination by dehydrogenating catalyst derivatives.



Scheme 4. Deprotection of the unseparable metathesis mixture from **4a** to obtain separable products **10**, **11**, and **12**.

Interestingly, when the reaction time of enyne **4a** metathesis was increased (6 days without more catalyst loading), the quantity of furan **7a** was magnified, leading to a ca. 2 : 1 mixture of **5a** and **7a**, respectively, and giving 43% of compound **10** and 25% of **11** after deprotection and purification of the mixture (yields from enyne). The ^{1}H NMR spectrum of derivative **11** clearly showed the characteristic signals of the furan ring at 6.17 and 7.31 ppm.

The formation of furan compounds (**7**) when using the first generation catalyst **1** was all the more surprising because, to our knowledge, side reactions involving dehydrogenation had yet never been described during metathesis reactions of oxo-derivatives. Some examples were reported in the pyrroline series and the pyrrole side products could not be formed in more than 30% yield, unless a dehydrogenation catalyst ($RuCl_3 \times H_2O$) was added.[7a] This report and others[7b,c] in the aza series mentioned that excessive heating might be responsible for the formation of the dehydrogenated products and that the presence of a basic amino group could favor this reaction. Indeed, we made observations in the same way, as overheating seemed to favor the formation of the furan.

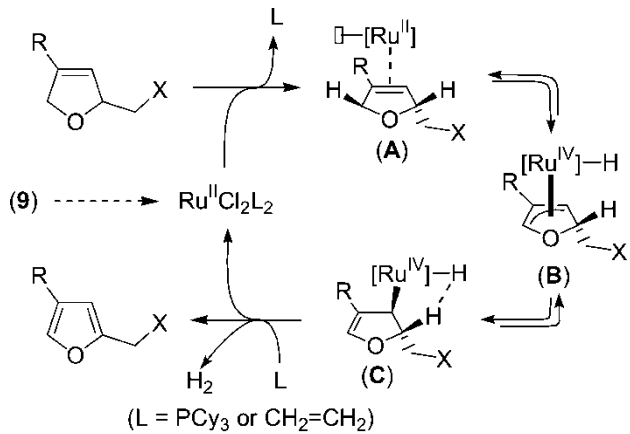
Neither spontaneous oxidation of the dihydrofuran **5a** in refluxing dichloromethane (air atmosphere) nor its dehydrogenation in the presence of fresh Grubbs' catalyst **1** and under ethylene atmosphere was possible. Thus, dehydrogenation must happen in the reaction mixture during enyne metathesis and could be catalyzed by a product of decomposition of the catalyst or of a catalytic intermediate resulting from excessive heating. The separation of the products from the ruthenium species usually proved to be difficult. As mentioned, we observed that in the case of purified but still catalyst-contaminated dihydrofuran **5a**, the furan **7a** was readily formed during the desilylation step; that could be consistent with the fact that basicity favors this reaction.[7a] As usual, elimination of all ruthenium contaminants after the metathesis steps is therefore very important.

The observation of cyclopropane side products led us to envisage a mechanism of dehydrogenation involving the ruthenium(II) complex $RuCl_2(PCy_3)_2$ which may result from reductive elimination from intermediate **9**.[2a] Some authors recently showed that this complex could also be formed by decomposition of the catalyst.[8] We then tried to transform the dihydrofuran **5a** in the presence of the related catalyst $RuCl_2(PPh_3)_3$, but no reaction could be observed. Even so, this experiment does not rule out the involvement of $RuCl_2(PCy_3)_2$.

Metathesis catalysts or derivatives are well known to give rise occasionally to olefin isomerization[9] that has been useful in the development of new tandem reactions to synthesize cyclic enol ethers.[10] Catalyst transformation or decomposition has been suspected by several authors in this process.[11] Particularly, hydridoruthenium species would be involved in these transformations.[10,12] For instance, the formation, isolation, and catalytic activity of ruthenium dihydride complex $RuCl_2(PCy_3)_2(H)_2$ has been discussed by Fürstner et al.[13] Other authors showed that upon treatment

with alcohols, catalysts **1** and **2** decompose into hydridocarbonyl–chloride complex $RuCl(L)_2(CO)(H)$ [L = ligands] with high catalytic activities.[10a,11b,11c,12] A number of these complexes are able to catalyze olefin isomerization. Grubbs recently isolated a diruthenium complex originated from thermal decomposition of the second-generation complex **2**.[11d] As already mentioned, $RuCl_2(L)_2$ complexes can be formed either from ruthenacyclobutane **9** or from ligand exchange ($PCy_3/CH_2{=}CH_2$) followed by dealkylidenation in a substrate-induced catalyst decomposition.[8] On the other hand, several transition-metal complexes [in particular $RuCl_2(PPh_3)_3$] have been reported to be effective catalysts for the hydrogenation of dihydrofurans under an atmosphere of hydrogen, but also as isomerization catalysts or more remarkably as disproportionation catalysts under an inert atmosphere, giving rise to equimolar amounts of furan and tetrahydrofuran derivatives.[14] Complex **1** itself is able to catalyze transfer hydrogenation from alcohols to ketones.[15] In our case, neither a tetrahydrofuran derivative possibly arising from disproportionation nor olefin isomerization could be observed.

In Scheme 5, we propose a mechanism for the dehydrogenation that could be promoted by a ruthenium(II) species, maybe $RuCl_2(PCy_3)_2$. After ligand exchange, the dihydrofuran compound would be engaged in the ruthenium(II) complex (**A**). Allylic insertion of ruthenium would lead to a transient π-allylhydridoruthenium(IV) intermediate (**B**) in equilibrium with (**C**). Reductive elimination of ruthenium from intermediate (**C**) would then lead to the dehydrogenated product. Hydrogen transfert on an alkene substrate during metathesis is unlikely as no hydrogenated product (tetrahydrofuran) could be detected and as dehydrogenation also happens in the absence of ethylene. We then suggest that molecular hydrogen is released during this transformation.



Scheme 5. Proposed mechanism for the dehydrogenation of dihydrofurans.

In conclusion, during our effort to synthesize 3-isopropenyldihydrofurans (**5a**, **b**) through enyne metathesis, we observed the formation of the corresponding isopropenylfurans (**7a**, **b**). These compounds certainly arose from in situ dehydrogenation of products **5a**, **b**. The involved catalytic species may result from heat-promoted decomposition of Grubbs' catalyst **1** in the reaction mixture. This is the first example of ring-closing enyne metathesis that gives rise to dehydrogenated products in the furan series.

EXPERIMENTAL SUPPORT

Typical procedure for the metathesis step: to a 0.1-M solution of the enyne in distilled (CaH_2) dichloromethane, catalyst **1** (0.1 eq) was added. Bubbling of ethylene was passed through the solution for 5 min and the mixture was refluxed for 16 h, keeping an atmosphere of ethylene under balloon pressure. After evaporation of the solvent, the crude mixture was purified by silica-gel chromatography (dichloromethane–heptane 1:1).

Enyne **4a** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 [*s*, 6H, $(CH_3)_2Si$], 0.86 [*s*, 9H, $(CH_3)_3CSi$], 1.61 [*m*, 4H, $(CH_2)_2$—CH_2OTBS], 1.85 (*t*, 3H, $J = 2.2$ Hz, CH_3—C≡C), 3.62 (*m*, 2H, CH_2OTBS), 3.82 (*m*, 1H, CH_2=CH—C*H*), 3.97 (*dq*, 1H, $J = 2.2$ Hz, $J = 15.0$ Hz), 4.15 (*dq*, 1H, $J = 2.2$ Hz, $J = 15.0$ Hz) (C≡C—CH_2—O), 5.20 (*m*, 1H, *trans* CH_2=CH—CH), 5.24 (*m*, 1H, *cis* CH_2=CH—CH), 5.65 (*m*, 1H, CH_2=C*H*—CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2, 117.6, 81.6, 79.8, 75.6, 62.9, 55.8, 31.5, 28.6, 26.0, 20.3, 3.6, −5.3. IR (CH_2Cl_2 solution): 2955–2857 (ν_{C-H}), 2242–2220 ($\nu_{C\equiv C}$), 1472, 1465, 1390, 1361, 1250 ($\nu_{Si\text{-}Me}$), 1099 ($\nu_{Si\text{-}O}$). HRMS (CI+, CH_4): m/z calculated for $C_{16}H_{31}O_2Si$ (MH^+): 283.2093; observed: 283.2097. R_f (heptane/AcOEt 7:3, Merck TLC plates 1.05554.0001):0.7.

Dihydrofuran **5a** (colorless oil): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 [*s*, 6H, $(CH_3)_2Si$], 0.87 [*s*, 9H, $(CH_3)_3CSi$], 1.59 [*m*, 4H, $(CH_2)_2$—CH_2OTBS], 1.91 (*s*, 3H, CH_3—C=CH_2), 3.61 (*m*, 2H, CH_2OTBS), 4.68 (large *s*, 1H, *trans* C=CH_2), 4.69 (*ddd*, 1H, $J = 2.0$ Hz, $J = 3.6$ Hz, $J = 11.4$ Hz), 4.77 (*ddd*, 1H, $J = 2.0$ Hz, $J = 5.2$ Hz, $J = 11.4$ Hz) (CH_2—O—CH), 4.91 (*m*, 1H, CH_2—O—C*H*), 4.95 (large *s*, 1H, *cis* C=CH_2), 5.71 (*m*, 1H, C=C*H*—). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.5, 136.4, 125.8, 113.9, 86.9, 74.5, 63.1, 32.3, 28.5, 26.0, 20.5, 18.3, −5.3. IR (CH_2Cl_2 solution): 2930–2853 ($\nu_{C\text{-}H}$), 1606 ($\nu_{C=C}$), 1475, 1389, 1260 ($\nu_{Si\text{-}Me}$), 1095 ($\nu_{Si\text{-}O}$). MS (ESI+): m/z 283.19 (MH^+). R_f (CH_2Cl_2/heptane 7:3): 0.3.

Furan **11** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59 (large *s*, 1H, O*H*), 1.88 (*quint.*, 2H, $J = 7$ Hz, CH_2—CH_2OH), 1.97 (*s*, 3H, CH_3—C=CH_2), 2.69 (*t*, 2H, $J = 7.4$ Hz, furan–CH_2), 3.67 (*t*, 2H, $J = 6.3$ Hz, CH_2OH), 4.86 (*s*, 1H), 5.13 (s, 1H) (CH_3—C=CH_2), 6.17 (*s*, 1H, *H*C=C—CH=C), 7.31 (*s*, 1H, HC=C—C*H*=C). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.4, 137.5, 135.2, 128.2, 110.3, 103.4, 61.9, 30.8, 24.3, 20.8. IR (CH_2Cl_2 solution):

3598, 3212, 3064, 2978, 1765, 1601, 1454. MS (ESI +): m/z 167.10 (MH^+). R_f (DCM/heptane 7:3): 0.2.

Cyclopropane **12** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73–0.96 (*m*, 3H, cyclopropane C*H*), 1.47–1.70 [*m*, 4H, (CH_2)$_2$—CH_2OH], 1.71 (*m*, 3H, CH_3—C═CH_2), 3.68 (*m*, 2H, CH_2OH), 3.78 (*d*, $J = 8.3$ Hz, 1H) and 3.91 (*m*, 2H) (CH_2—O—C*H*), 4.75 and 4.85 (2 *m*, 2H CH_3—C═CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.1, 110.8, 80.9, 69.2, 63.0, 31.9, 31.5, 29.7, 28.4, 20.8, 14.4. IR (CH_2Cl_2 solution): 3687, 3023, 3003, 2991, 2928, 2862, 1634, 1609, 1450, 1380, 1250, 1120, 1040, 1019. HRMS (CI+, CH_4): m/z calculated for $C_{11}H_{19}O_2$ (MH^+): 183.1385; observed: 183.1383. R_f (CH_2Cl_2/heptane 7:3): 0.1.

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